GlaxoSmithKline Inc.
5 Moore Drive
Research Triangle Park, NC 27709

ANORO™ ELLIPTA™ (Umeclidinium Bromide/Vilanterol Inhalation Powder) For Treatment of Chronic Obstructive Pulmonary Disease

NDA 203975

FDA Advisory Committee Briefing Document

Presented to:

Pulmonary-Allergy Drug Advisory Committee

September 10, 2013

ADVISORY COMMITTEE BRIEFING MATERIALS:

AVAILBLE FOR PUBLIC RELEASE

TABLE OF CONTENTS

PAGE

List of Figures

PAGE

List of Tables

Abbreviations

AC	active-comparator
ADVAIR	fluticasone propionate/salmeterol inhalation powder
AE	adverse event
AESI	adverse event of special interest
ANORO	umeclidinium bromide/vilanterol inhalation powder
ATS	American Thoracic Society
AUC	area under the curve
BD	twice daily
BREO	fluticasone furoate/vilanterol inhalation powder
CDC	copy differences from control
CI	confidence interval
CLcr	creatinine clearance
C_{max}	maximum concentration
COPD	chronic obstructive pulmonary disease
CR	copy reference
CV	cardiovascular
DB	double-blind
DPI	dry powder inhaler
ECG	electrocardiogram
EET	exercise endurance time
ESWT	exercise shuttle walk test
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FF	fluticasone furoate
FRC	functional residual capacity
FVC	forced vital capacity
GOLD	Global Initiative for Obstructive Lung Disease
GSK	GlaxoSmithKline
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
ICSR	individual case safety report
IH	Inhalation/ inhaled
IND	Investigational New Drug
ISWT	incremental shuttle walk test
ITT	intent-to-treat
IV	intravenous
J2R	jump to reference
kg	kilogram
L	liter
LABA	long-acting $beta_2$-agonist
LAMA	long-acting muscarinic antagonist
LMCF0	last mean carried forward assuming 0 mL/year decline
LMCF25	last mean carried forward assuming 25 mL/year decline

LRTI	lower respiratory tract infection
LS	least squares
MACE	Major Adverse Cardiac Event
MAR	missing at random
MCID	minimally clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mMRC	modified Medical Research Council
MMRM	mixed model repeated measures
msec	millisecond
NA	not applicable
NDA	New Drug Application
NHANES	National Health and Nutrition Examination Survey
OL	open label
PC	placebo-controlled
PD	pharmacodynamic
PG	parallel group
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PLA	placebo
PO	orally
PT	preferred term
QD	once-daily
QTc(F)	QT interval corrected for heart rate by Fridericia's formula
R	randomized
SAE	serious adverse event
SD	standard deviation
SE	standard error
SGRQ	St. George's Respiratory Questionnaire
SMQ	standard MedDRA query
SOBDA	shortness of breath with daily activities
Spiriva	tiotropium bromide inhalation powder
$t_{1/2}$	terminal phase half-life
TDI	transition dyspnea index
TFH	twenty-four hour
TIO	tiotropium bromide
t_{max}	time of occurrence of C_{max}
Tudorza	aclidinium bromide inhalation powder
UMEC	umeclidinium bromide
US	United States
URTI	upper respiratory tract infection
VI	vilanterol
XO	cross-over

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ADVAIR
ANORO
BREO
DISKUS
ELLIPTA
SEREVENT

Trademarks not owned by the GlaxoSmithKline group of companies
Combivent
DuoNeb
HandiHaler
Spiriva HandiHaler
Tudorza Pressair

1. EXECUTIVE SUMMARY

1.1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease that is both preventable and treatable. A key feature of COPD is airflow obstruction that progressively worsens with time, leading to breathlessness and other debilitating symptoms [GOLD, 2013]. These symptoms can lead to limitations in physical functioning and impairment of quality of life. COPD is a significant public health challenge and remains a leading cause of morbidity and mortality in the United States (US), affecting an estimated 27 million Americans.

Bronchodilator medications are the mainstay of pharmacologic therapy for COPD to improve the airflow obstruction which characterizes the disease. These medications are commonly used on a regular basis to improve symptoms, exercise limitation, and health status [GOLD, 2013]. The predominant classes of inhaled bronchodilators are muscarinic receptor antagonists and $beta_2$-agonists. These 2 classes of bronchodilators relax airway smooth muscle and improve airflow obstruction through distinct and complementary mechanisms of action, thereby providing a scientific rationale for combination products to optimize bronchodilation. Combination products containing the short-acting $beta_2$-agonist albuterol and the short-acting anticholinergic ipratropium (i.e., Combivent and DuoNeb) are widely used for the treatment of airflow obstruction associated with COPD. However, they are limited by frequent dosing (i.e., up to 4 times per day).

Long-acting muscarinic antagonists (LAMAs) and long-acting $beta_2$-agonists (LABAs) are available as separate products and are recommended over short-acting bronchodilators for the maintenance treatment of moderate to very severe COPD as they are more efficacious and convenient to use than the shorting acting agents [Celli, 2004; GOLD, 2013]. Although studies have shown that co-administration of LAMAs and LABAs from separate inhalers is more effective than either drug class alone in managing stable COPD to improve lung function, symptoms and health status and that the safety profile of the combinations is similar to that of the long-acting bronchodilator monotherapies [Cazzola, 2004; Cazzola, 2005;Van Noord, 2005; Van Noord, 2006; Tashkin, 2008], no fixed-dose LAMA/LABA combination products are currently approved for COPD treatment in the US.

GlaxoSmithKline (GSK) has developed a once-daily fixed-dose LAMA/LABA combination product (ANORO™ ELLIPTA™ [umeclidinium bromide/vilanterol inhalation powder]) aimed to optimize bronchodilator response. In addition, it has the potential to offer improved convenience and compliance over the use of single long-acting bronchodilators from separate inhalers.

Umeclidinium (UMEC), the LAMA component, is a new molecular entity. A New Drug Application (NDA) for UMEC inhalation powder (monotherapy) was submitted to the US Food and Drug Administration (FDA) on 30 April 2013. Vilanterol (VI), the LABA component, is a component of the inhaled corticosteroid (ICS)/LABA combination product containing fluticasone furoate (FF) and VI (BREO™ ELLIPTA™ [fluticasone furoate/vilanterol inhalation powder]). BREO ELLIPTA received approval by the US FDA for the treatment of COPD on 10 May 2013. Vilanterol is not currently approved for marketing as a monotherapy.

A NDA in support of ANORO ELLIPTA for the long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema, was submitted to the FDA on 18 December 2012.

1.2. Product Information

Umeclidinium/vilanterol is administered by an innovative, single-step activation, multi-dose dry powder inhaler (DPI) (ELLIPTA). Two, double-foil, laminate, blister strips each with 30 blisters are contained within the inhaler to provide a total of 30 doses of UMEC/VI. One strip contains a blend of micronized UMEC with magnesium stearate and lactose as excipients. The second strip contains a blend of micronized VI with magnesium stearate and lactose as excipients. When actuated, the ELLIPTA inhaler simultaneously delivers the contents of a single blister from each of the 2 blister strips.

1.3. Clinical Pharmacology

A total of 40 clinical studies have been conducted evaluating the clinical pharmacology of UMEC/VI and the UMEC and VI monotherapies. Studies conducted with UMEC alone or VI alone included administration by the inhaled (IH), intravenous (IV), and oral (PO) routes. These studies were conducted predominantly in healthy subjects but also included subjects with COPD, subjects with moderate hepatic impairment, and subjects with severe renal impairment.

When UMEC and VI were administered in combination by the inhaled route, the pharmacokinetic (PK) parameters for each component were similar to those observed when each was administered separately. The PK profile for UMEC/VI is consistent with inhaled medications with limited systemic exposure and rapid clearance. No dose adjustment for renal or hepatic impairment, age, gender, weight, ethnicity, or concomitant ICS use is warranted.

1.4. Overview of Clinical Development Program

The UMEC/VI global clinical development program was constructed to evaluate the safety and efficacy of UMEC/VI in improving lung function and symptoms across a broad range of patients with COPD. As the development program was undertaken prior to approval of either component as a monotherapy, studies designed to evaluate the efficacy of both UMEC and VI individually and the UMEC/VI combination, as well as the contribution of each component to the combination were included. Safety was assessed for UMEC/VI, UMEC, and VI compared with placebo as well as for UMEC/VI compared with UMEC and VI individually. In addition, the clinical development program included comparisons of UMEC/VI with tiotropium via the Handihaler, an approved LAMA with a well established efficacy and safety profile.

Phase II studies conducted to support UMEC and VI monotherapy dose selection and dosing interval are summarized in Table 1. Phase III UMEC/VI studies are summarized in Table 2. For brevity, the trials are identified by the last 3 digits of the study number for the remainder of this document (e.g., study DB2113361 is annotated as study 361).

Table 1 UMEC and VI Dose-Ranging and Dosing-Interval Studies

Study Number	Study Design	Duration	Treatment Groups (mcg) (once-daily unless otherwise specified): Number of Subjects in ITT population	Population
UMEC Dose-Ranging and Dosing-Interval Studies				
AC4113073	R, DB, XO, PC Incomplete block	3 periods per subject, 14 days per period	PLA: N=158 Once-daily: UMEC 62.5: N=35 UMEC 125: N=34 UMEC 250: N=36 UMEC 500: N=38 UMEC 1000: N=32 TIO 18 OL: N=35 Twice-daily: UMEC 62.5: N=34 UMEC 125: N=37 UMEC 250: N=33	COPD
AC4115321	R, DB, XO, PC Incomplete block	3 periods per subject, 7 days per period	PLA: N=60 Once-daily: UMEC 15.6: N=60 UMEC 31.25: N=57 UMEC 62.5: N=59 UMEC 125: N=60 TIO 18 OL: N=56 Twice-daily: UMEC 15.6: N=56 UMEC 31.25: N=58	COPD
AC4113589	R, DB, PG, PC	28 days	PLA: N=71 UMEC 125: N=71 UMEC 250: N=72 UMEC 500: N=71	COPD
VI Dose-Ranging and Dosing-Interval Studies				
B2C111045	R, DB, PG, PC Stratified	28 days	PLA: N=101 Once-daily: VI 3: N=99 VI 6.25: N=101 VI 12.5: N=101 VI 25: N=101 VI 50: N=99	COPD
HZA113310	R, DB, XO, PC	5 periods per subject, 7 days per period	PLA: N=74 Once-daily: VI 6.25: N=73 VI 12.5: N=73 VI 25: N=73 Twice-daily: VI 6.25: N=74	Asthma
B2C109575	R, DB, PG, PC Stratified	28 days	PLA: N=102 VI 3: N=101 VI 6.25: N=101 VI 12.5: N=100 VI 25: N=101 VI 50: N=102	Asthma

Abbreviations: COPD=chronic obstructive pulmonary disease; DB=double-blind; ITT=intent-to-treat; OL=open-label; PC=placebo-controlled; PG=parallel-group, PLA=placebo; R=randomized, TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol; XO=cross-over

Table 2 Phase III UMEC/VI Studies

Study	Study Design	Key Inclusion Criteria	Once-Daily Treatment (mcg)	N (ITT)	Primary/Secondary Efficacy Endpoints or Co-Primary Endpoint
Primary Efficacy Studies: Placebo-Controlled					
DB2113373	R, DB, PG, PC 24 Weeks	• Post bronchodilator FEV_1/FVC ratio <0.70 • Post bronchodilator FEV_1 ≤70% predicted [a] • mMRC dyspnea score ≥2	UMEC/VI 62.5/25 UMEC 62.5 VI 25 Placebo	413 418 421 280 Total = 1532	Trough FEV_1 at Day 169 (Week 24) 0 to 6 hour weighted mean FEV_1 at Day 168
DB2113361	R, DB, PG, PC 24 Weeks	• Post bronchodilator FEV_1/FVC ratio <0.70 • Post bronchodilator FEV_1 ≤70% predicted [a] • mMRC dyspnea score ≥2	UMEC/VI 125/25 UMEC 125 VI 25 Placebo	403 407 404 275 Total = 1489	Trough FEV_1 at Day 169 (Week 24) 0 to 6 hour weighted mean FEV_1 at Day 168
Primary Efficacy Studies: Active-comparator					
DB2113360	R, DB, PG, AC 24 Weeks	• Post bronchodilator FEV_1/FVC ratio <0.70 • Post bronchodilator FEV_1 ≤70% predicted [a] • mMRC dyspnea score ≥2	UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 TIO	214 212 209 208 Total = 843	Trough FEV_1 at Day 169 (Week 24) 0 to 6 hour weighted mean FEV_1 at Day 168
DB2113374	R, DB, PG, AC 24 Weeks	• Post bronchodilator FEV_1/FVC ratio <0.70 • Post bronchodilator FEV_1 ≤70% predicted [a] • mMRC dyspnea score ≥2	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 TIO	215 217 222 215 Total = 869	Trough FEV_1 at Day 169 (Week 24) 0 to 6 hour weighted mean FEV1 at Day 168
Long-term Safety Study					
DB2113359	R, DB, PG, PC 52 Weeks	• Post bronchodilator FEV_1/FVC ratio <0.70 • Post bronchodilator FEV_1 ≥35 and ≤80% predicted [a]	UMEC/VI 125/25 UMEC 125 Placebo	226 227 109 Total = 562	No efficacy endpoints were specified; however, pre-specified safety endpoints of trough FEV_1, rescue albuterol use and COPD exacerbations are supportive of efficacy

Study	Study Design	Key Inclusion Criteria	Once-Daily Treatment (mcg)	N (ITT)	Primary/Secondary Efficacy Endpoints or Co-Primary Endpoint
Exercise/Lung Function Studies					
DB2114417	R, DB, PC, XO Incomplete block 12 Weeks per period; 2 periods per subject	• FRC of ≥120% of predicted normal • Post bronchodilator FEV_1 ≥35 and ≤70% predicted [e] • mMRC dyspnea score ≥2 • Post bronchodilator FEV_1/FVC ratio <0.70	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 UMEC 62.5 VI 25 Placebo	144 152 50 49 76 170 Total = 348	Co-primary endpoints: EET postdose at Week 12 Trough FEV_1 at Week 12
DB2114418	R, DB, PC, XO Incomplete block 12 Weeks per period; 2 periods per subject	• FRC of ≥120% of predicted normal • Post bronchodilator FEV_1 ≥35 and ≤70% predicted [a] • mMRC dyspnea score ≥2 • Post bronchodilator FEV_1/FVC ratio <0.70	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 UMEC 62.5 VI 25 Placebo	128 130 41 40 64 151 Total = 307	Co-primary endpoints: EET postdose at Week 12 Trough FEV_1 at Week 12

Abbreviations: AC=active comparator; DB=double-blind; EET=exercise endurance time; FEV_1=forced expiratory volume in 1 second; FRC=functional residual capacity; FVC=forced vital capacity; ITT=intent-to-treat; mMRC=modified Medical Research Council; NHANES=National Health and Nutrition Examination Survey PC=placebo-controlled; PG=parallel-group; R=randomized; UMEC=umeclidinium bromide, VI=vilanterol; XO=cross-over.
Note: All treatments were administered once daily in the morning via the ELLIPTA dry powder inhaler.
a. FEV_1 percent predicted calculated using NHANES III reference equations [Hankinson, 1999; Hankinson, 2010]

1.5. UMEC and VI Dose and Dosing-Interval Selection

Six dose-ranging studies of 7 to 28 days duration were conducted for UMEC and VI separately to support the selection of the appropriate dose for the monotherapies and as components of UMEC/VI (Table 1). Two UMEC studies and one VI study included comparisons of once- and twice-daily dosing in order to evaluate dosing interval.

In the 3 UMEC ranging studies, doses ranging from 15.6 mcg to 1000 mcg once daily, representing a 64-fold range, were evaluated in subjects with COPD. Doses of 125 mcg and below had adverse event (AE) profiles that were comparable with placebo, while at doses of 250 mcg and above, AEs of headache, dry mouth, and cough were more frequent.

Results of the statistical analysis of trough forced expiratory volume in one second (FEV_1) (primary endpoint) from these studies are shown in Table 3. The bronchodilator response appeared consistent over the range of treatment durations tested in these studies (7 to 28 days), indicating that the steady-state pharmacodynamic (PD) effect of UMEC is observed at most after 7 days of treatment (corresponding to trough FEV_1 at Day 8).

Considering the data across studies, a dose ordering for trough FEV_1 was observed (Table 3). The dose of 125 mcg provided a near maximal response in these studies. The 62.5 mcg appeared to be on the ascent of the dose response with lower doses providing less improvement. To further evaluate the efficacy and safety of UMEC in larger, longer term studies, 2 doses of UMEC were selected for Phase III. The dose of 125 mcg was selected as it provided near maximal efficacy, and a lower dose of 62.5 mcg was also selected.

Table 3 LS Mean Difference from Placebo for Change from Baseline for Trough FEV_1 (Studies 073, 321, and 589)

Study/Day	LS Mean Difference from Placebo for Change from Baseline in Trough FEV_1 (mL) (95% CI) [n]							
	Once-daily UMEC dose (mcg)							
	15.6	31.25	62.5	125	250	500	1000	TIO [a]
073 at Day 15			128 (60, 196) [34]	147 (77, 216) [33]	95 (27, 162) [35]	140 (74, 205) [37]	186 (113, 259) [29]	105 (37, 173) [34]
321 at Day 8	113 (58,168) [58]	101 (45,158) [56]	124 (68,179) [59]	183 (127,239) [59]				101 (45,157) [56]
589 at Day 29				159 (088,229) [64]	168 (99,238) [68]	150 (80,220) [64]		

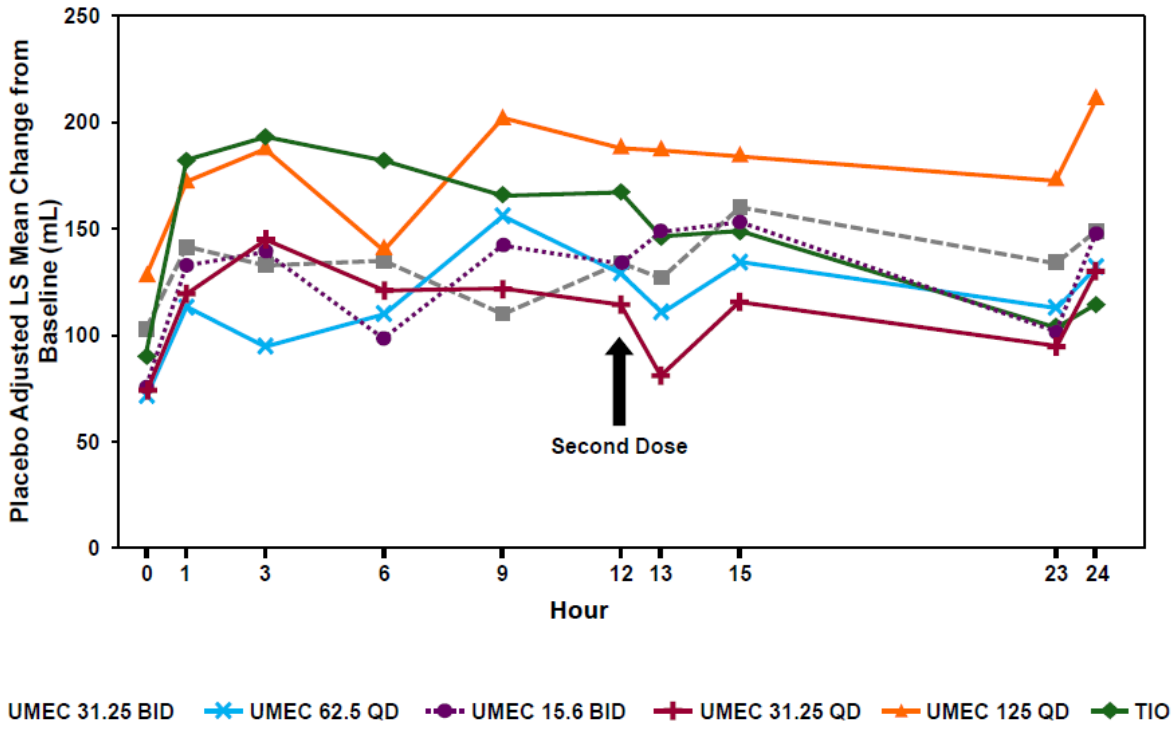
Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; TIO=tiotropium; UMEC=umeclidinium bromide

Note: Studies 073 and 321 were cross-over studies.

a. Tiotropium was administered open-label.

The 24 hour serial FEV_1 profiles for study 321 allow for comparisons of the total daily UMEC dose administered once daily or administered as 2 divided doses and for comparison with tiotropium. The serial FEV_1 profile with once daily dosing showed consistent improvements in FEV_1 relative to placebo over 24 hours (Figure 1). Twice daily dosing of UMEC at the same nominal dose did not provide substantially greater benefit over once-daily dosing in the latter 12 hours of the dosing interval. Notably, administration of a second dose of UMEC at 12 hours following the morning dose did not result in an appreciable change in FEV_1 in the subsequent 12 hours. Furthermore, the improvements compared with placebo in FEV_1 observed at time points over the first 12 hours were maintained at time points over the second 12 hours with UMEC once daily.

Figure 1 **Placebo-Adjusted LS Mean Change from Baseline for Trough FEV_1 Over Time on Day 7: UMEC Once-Daily and Twice-Daily Doses and Tiotropium (Study 321)**



Abbreviations: BID=twice-daily, CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; QD=once daily; TIO=tiotropium; UMEC=umeclidinium bromide

The VI dose and dosing interval (25 mcg once-daily), selected based on dose-ranging studies in COPD and asthma (a population highly responsive to bronchodilation), is the same as the dose in the BREO ELLIPTA combination product which is approved in the US for the treatment of COPD.

1.6. Clinical Efficacy

A comprehensive clinical development program was conducted that evaluated approximately 6000 subjects across all Phase III studies. Key features of the 7 Phase III UMEC/VI studies are shown in Section 1.4, Table 2. The 4 Primary Efficacy Studies provide key efficacy data supporting the lung function claim and persistence of efficacy. The primary and secondary efficacy endpoints in these studies are recommended and accepted in international treatment guidelines [GOLD, 2013] and in regulatory guidance and are considered important to the COPD patient. The 2 Exercise/Lung Function studies provide supportive lung function efficacy data.

The Phase III development program was designed to investigate 2 doses of UMEC/VI, 62.5/25 and 125/25 mcg. The 2 doses of UMEC/VI were demonstrated to be similar with regard to efficacy and safety in the overall Phase III study population. As part of pre-planned subgroup

analyses, the subpopulation of subjects demonstrating reversibility to albuterol (approximately 30% of enrolled subjects) showed greater benefit with the higher dose based on lung function. As a result of this finding and further post-hoc analyses, both doses of UMEC/VI were initially proposed in the NDA. During the NDA review, revised labeling was submitted for the lower strength only, as the subpopulation requires further delineation. The data for the higher dose are presented as they provide important information regarding the overall efficacy and safety of the UMEC/VI combination at double the UMEC dose.

1.6.1. Primary Efficacy Studies

The primary efficacy studies were comprised of 2 placebo-controlled studies (studies 373 and 361) and 2 active-comparator studies (studies 360 and 374). All 4 Primary Efficacy Studies were randomized, multicenter, parallel-group studies with a 24-week treatment period. The UMEC/VI, UMEC and VI doses evaluated in each study are shown in Table 4. All treatments were administered once-daily in the morning. The contribution of UMEC 62.5 mcg to the efficacy of UMEC/VI 62.5/25 (by comparison of UMEC/VI 62.5/25 mcg vs. VI 25 mcg) was evaluated in study 373 and study 360. The contribution of VI 25 mcg (by comparison of UMEC/VI 62.5/25 mcg vs. UMEC 62.5 mcg) was evaluated in study 373. Comparisons of UMEC and VI with placebo in studies 373 and 361 provide the principal data to evaluate the safety and efficacy of the component monotherapies. Supportive lung function data are also provided from the Exercise/Lung Function studies (Section 1.6.2).

Table 4 Treatment Groups: Primary Efficacy Studies

Placebo-controlled Studies	
Study 373	Study 361
UMEC/VI 62.5/25 mcg	UMEC/VI 125/25 mcg
UMEC 62.5 mcg	UMEC 125 mcg
VI 25 mcg	VI 25 mcg
Placebo	Placebo
Active-comparator Studies	
Study 360	Study 374
UMEC/VI 125/25 mcg	UMEC/VI 125/25 mcg
UMEC/VI 62.5/25 mcg	UMEC/VI 62.5/25 mcg
VI 25 mcg	UMEC 125 mcg
Tiotropium	Tiotropium

Abbreviations: UMEC=umeclidinium bromide; VI=vilanterol

In the placebo-controlled trials, UMEC/VI, UMEC, VI and matching placebo were administered in a double-blind fashion once daily in the morning via the ELLIPTA DPI.

A double dummy design was used for the active-comparator studies because these studies included delivery with the ELLIPTA DPI and the HandiHaler DPI. Blister packaged capsules of tiotropium or its corresponding placebo were administered once daily in the morning via the HandiHaler DPI and UMEC/VI, UMEC, VI or placebo were administered once daily in the morning via the ELLIPTA DPI. Each patient took one dose from the Handihaler DPI and one dose from the ELLIPTA DPI each morning. Blinding of tiotropium was imperfect, however, because the tiotropium capsules had trade markings but the placebo capsules, while closely

matched in color, did not have trade markings. Whether patients would notice, and rightly or wrongly attach any significance to the capsule markings, is unclear. As these studies were of parallel group design, the capsule type was consistent for each patient for the duration of the study. Both the tiotropium and placebo blister packages were covered with opaque over-labels with the intent of shielding information appearing on the blister packaging of tiotropium. The HandiHaler DPIs were covered with labels in order to mask identifying marks on the inhaler. Dosing in the clinic was administered without the presence of staff involved with safety and efficacy assessments to guard against the possibility that they would observe and draw correct inferences from the presence or absence of markings on capsules removed from the blisters.

Patients were eligible for participation in these studies if they were 40 years or older with a clinical history of COPD (as defined by the American Thoracic Society [ATS]/European Respiratory Society [Celli, 2004]), an extensive cigarette smoking history (≥10 pack-years), a post-albuterol FEV_1 of ≤70% of predicted normal values and a post-albuterol FEV_1/forced vital capacity (FVC) ratio of <0.70, and symptoms upon entry based on a modified Medical Research Council (mMRC) dyspnea score of ≥2. Exclusion criteria for clinically significant medical conditions as determined by the investigator and other respiratory conditions including a current history of asthma which could confound assessment of efficacy or safety were applied across these studies. The inclusion and exclusion criteria for these studies were similar to those used in registration programs for other long-acting bronchodilators.

Concurrent use of ICS at a stable dose and as-needed use of short-acting bronchodilators were permitted to provide adequate background pharmacotherapy for COPD.

Spirometry assessments were performed multiple times during the 6 month treatment period with the final assessment at Week 24. Subjects were required to be withdrawn from the study if they experienced a clinically important laboratory, 12-lead electrocardiogram (ECG), or Holter finding. Additionally, subjects were to be withdrawn from the study if they experienced a COPD exacerbation (defined as an acute worsening of symptoms of COPD requiring the use of any treatment other than study medication or rescue albuterol).

For all 4 studies, the primary efficacy endpoint was trough FEV_1 on Day 169 and the secondary endpoint was 0 to 6 hour post-dose weighted mean FEV_1 on Day 168. Trough FEV_1 was chosen as the primary endpoint to evaluate efficacy at the end of the once-daily dosing interval while 0 to 6 hour weighted mean was included to evaluate efficacy over the initial phase of the dosing interval. Other supportive endpoints included rescue albuterol use and the St. George's Respiratory Questionnaire (SGRQ) to assess impact on health-related quality of life.

Safety assessments included the reporting of AEs, routine clinical laboratory assessments, evaluation of vital signs, and 12-lead ECG measurements. Holter monitoring was obtained in a subset of subjects in the placebo-controlled studies.

1.6.1.1. Subject Disposition

In the integrated Primary Efficacy Studies, at least 70% of subjects in each treatment group completed the study. The most common reasons for withdrawal were lack of efficacy (7%) and

AE (6%). The reasons for withdrawal across treatment groups were consistent except for a larger proportion of subject withdrawals in the placebo group because of lack of efficacy.

1.6.1.2. Demographics and Baseline Characteristics

The demographic and baseline characteristics of the population in the Primary Efficacy Studies is representative of a broad range of patients with COPD. The mean age was 63.3 years and more males (68%) than females were enrolled. The predominant race category was White (84%). Overall, 3% of subjects were of African Heritage/African American. In the US, approximately 10% of subjects were African American.

Approximately half (49%) of the subjects in the Primary Efficacy Studies were current smokers and approximately half (49%) were using concurrent ICS therapy. Subjects had moderate to very severe COPD based on baseline percent predicted FEV_1 values. Thirty-one percent of subjects were reversible to albuterol (defined as an improvement in FEV_1 following administration of a short-acting bronchodilator of ≥12% and ≥200 mL from pre-treatment levels). The majority of subjects (72%) did not report a COPD exacerbation requiring oral corticosteroids or antibiotics in the year prior to Screening visit.

1.6.1.3. Lung Function

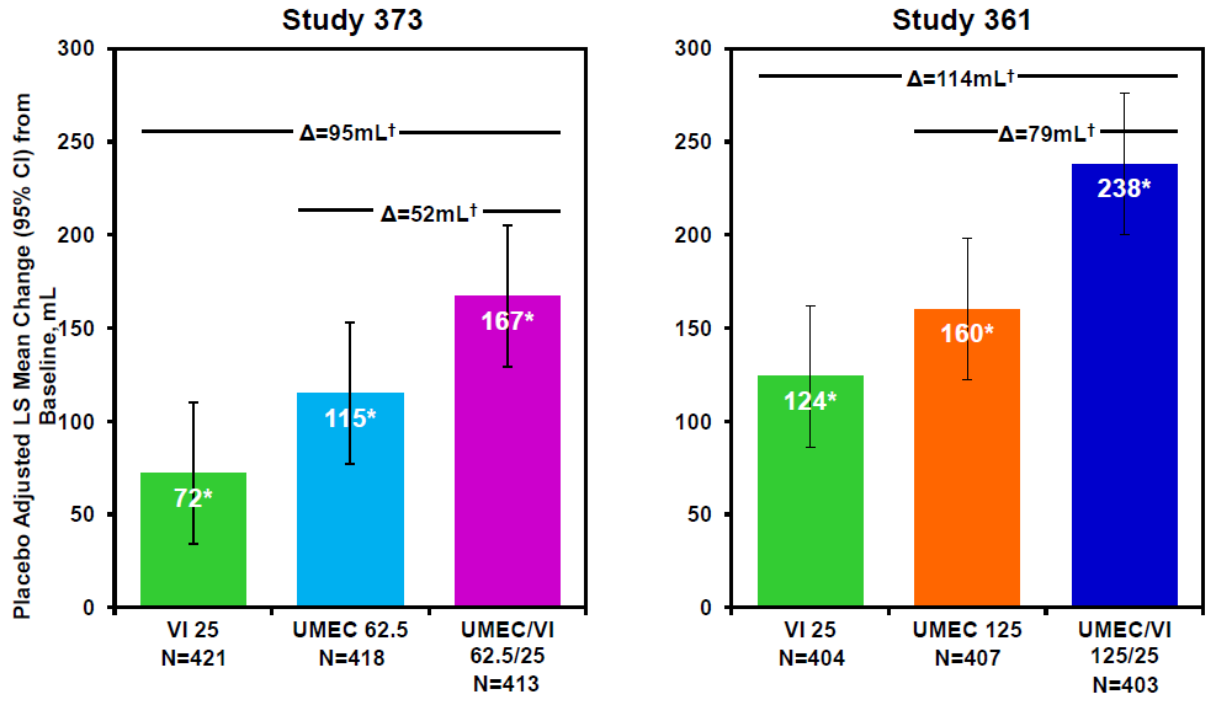
Data for trough FEV_1 at Day 169 (primary endpoint) and 0 to 6 hour weighted mean FEV_1 at Day 168 (secondary endpoint) are presented for the placebo-controlled studies and then the active-comparator studies.

Placebo-controlled Studies

Both doses of UMEC/VI (62.5/25 and 125/25 mcg) and the UMEC (62.5 and 125 mcg) and VI 25 mcg monotherapies demonstrated statistically significant and clinically meaningful increases in trough FEV_1 at Day 169 (primary endpoint) compared with placebo (Figure 2).

For comparisons with components, both doses of UMEC/VI (62.5/25 and 125/25 mcg) demonstrated statistically significant and clinically meaningful increases in trough FEV_1 at Day 169 compared with respective component doses of UMEC (62.5 and 125 mcg) and VI 25 mcg, confirming that both of the components contribute to efficacy of the UMEC/VI combination at the end of the dosing interval.

Figure 2 Placebo-Adjusted LS Mean Change from Baseline for Trough FEV_1 (mL) at Day 169 (Studies 373 and 361)



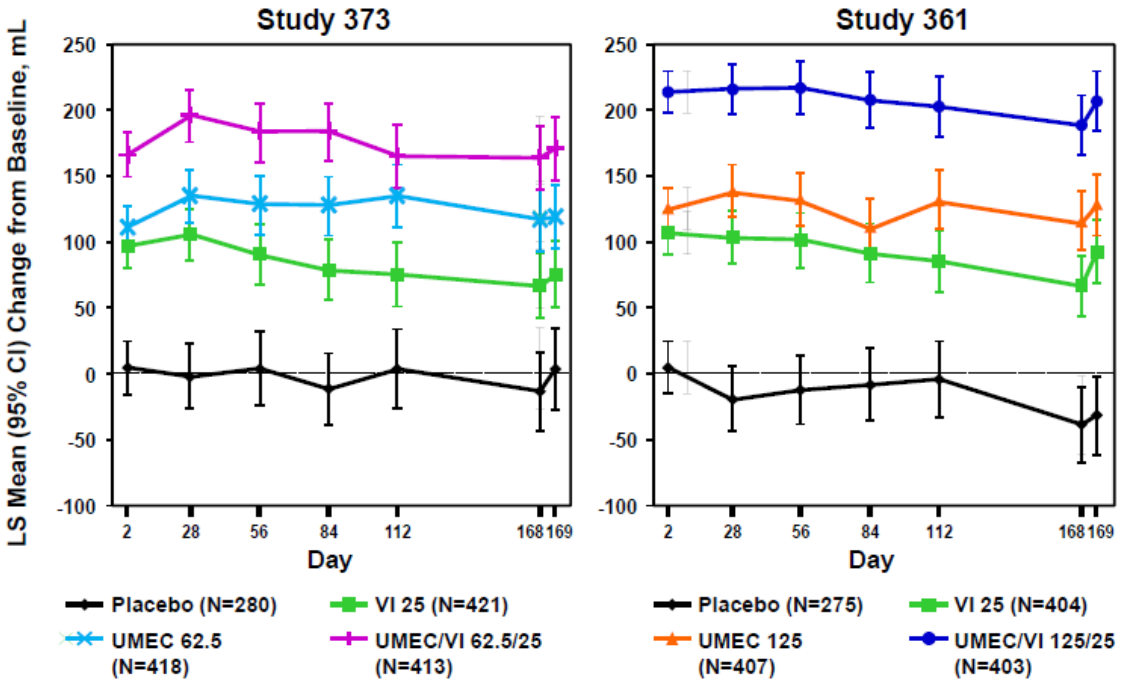
*p<0.001 vs. placebo
† p≤0.004 for UMEC/VI 62.5/25 vs. UMEC 62.5 and VI and for UMEC/VI 125/25 vs. UMEC 125 and VI 25

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; UMEC=umeclidinium bromide; VI=vilanterol

Beginning at Day 2 and continuing throughout the study, UMEC/VI (62.5/25 and 125/25 mcg), UMEC (62.5 and 125 mcg) and VI 25 mcg demonstrated statistically significant increases in trough FEV_1 compared with placebo (Figure 3). For comparisons with components, both doses of UMEC/VI (62.5/25 and 125/25 mcg) exhibited statistically significant increases in trough FEV_1 at all assessments throughout the study compared with respective component doses of UMEC (62.5 and 125 mcg) and VI 25 mcg, except for UMEC/VI 62.5/25 mcg vs. UMEC

62.5 mcg at Day 112. This demonstrates the efficacy of both doses of UMEC/VI at the end of the 24-hour dosing interval and shows that the effect at trough is consistent over time.

Figure 3: LS Mean Change from Baseline for Trough FEV_1 (mL) over 24 Weeks (Studies 373 and 361)



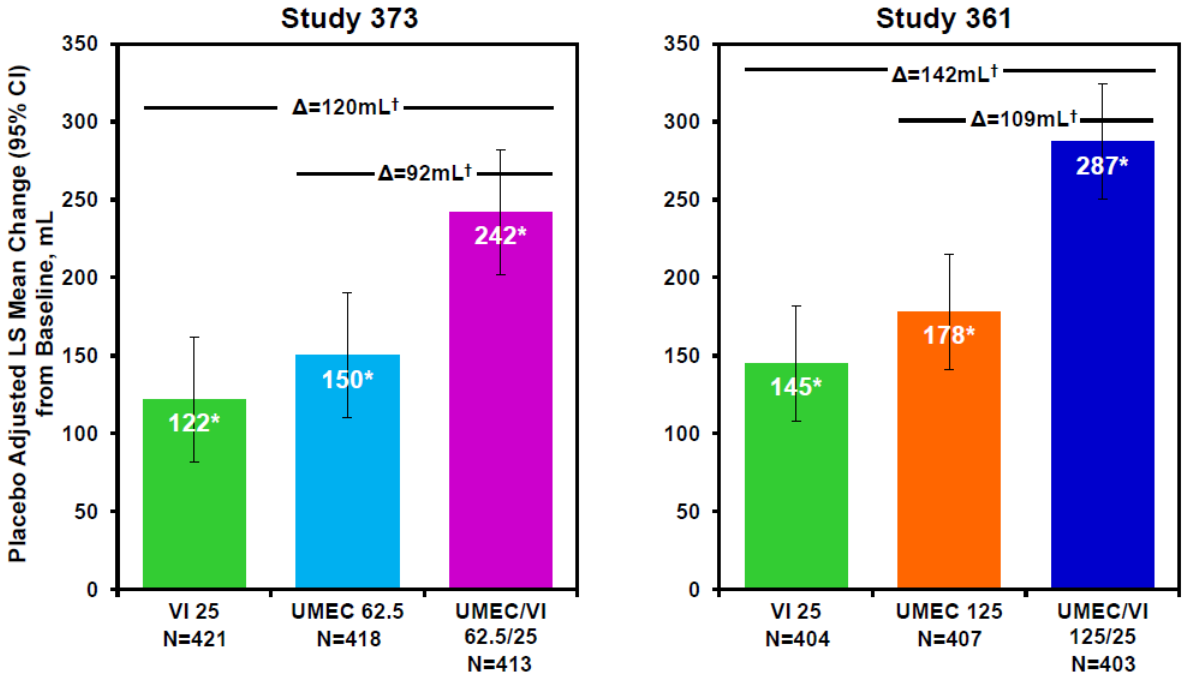
p<0.001 for all comparisons of UMEC/VI (62.5/25 and 125/25), UMEC (62.5 and 125), VI with placebo
p≤0.006 for all comparisons of UMEC/VI (62.5/25 and 125/25) with monotherapies, except UMEC/VI 62.5/25 vs UMEC 62.5 at Day 112 (p=0.076)

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; UMEC=umeclidinium bromide; VI=vilanterol

Both doses of UMEC/VI (62.5/25 and 125/25 mcg) and the UMEC (62.5 and 125 mcg) and VI 25 mcg monotherapies demonstrated statistically significant increases in 0 to 6 hour weighted mean FEV_1 at Day 168 (secondary endpoint) compared with placebo (Figure 4).

For comparisons with components, both doses of UMEC/VI (62.5/25 and 125/25 mcg) demonstrated statistically significant increases in 0 to 6 hour weighted mean FEV_1 at Day 168 compared with respective component doses of UMEC (62.5 and 125 mcg) and VI 25 mcg, confirming that both of the components contribute to efficacy of the UMEC/VI combination over the initial portion of the dosing interval and providing additional evidence for the contribution of UMEC and VI to the combination.

Figure 4 **Placebo-Adjusted LS Mean Change from Baseline for 0 to 6 hour Weighted Mean FEV_1 (mL) at Day 168 (Studies 373 and 361)**



*p<0.001 vs. placebo

† p<0.001 for UMEC/VI 62.5/25 vs. UMEC 62.5 and VI and for UMEC/VI 125/25 vs. UMEC 125 and VI 25

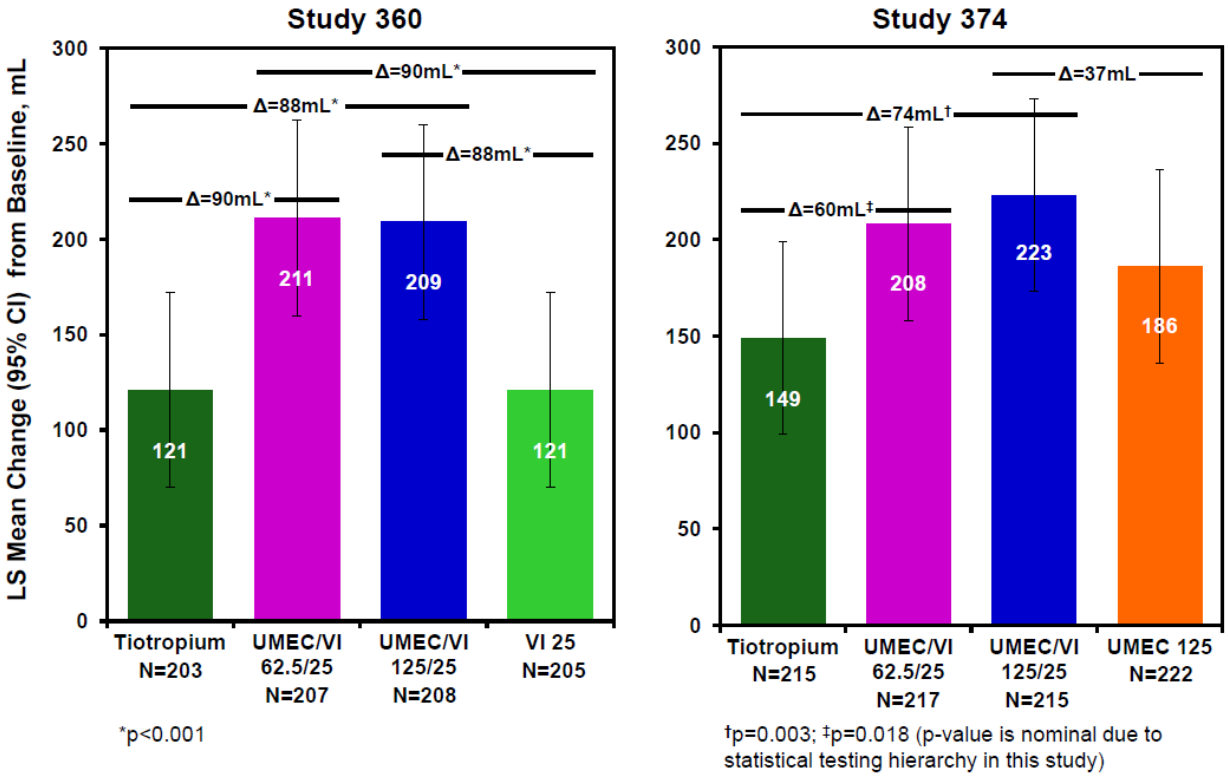
Abbreviations: FEV_1=forced expiratory volume in 1 second; LS=least squares; UMEC=umeclidinium bromide; VI=vilanterol

Active-comparator Studies

In study 360, statistically significant increases in trough FEV_1 at Day 169 were demonstrated for comparisons of UMEC/VI 62.5/25 and 125/25 mcg with VI 25 mcg (Figure 5), further demonstrating the contribution of UMEC to the combination. In study 374, comparisons of UMEC/VI 62.5/25 mcg and 125/25 mcg with UMEC 125 mcg for trough FEV_1 at Day 169 were not statistically significant. The finding for the comparison of UMEC/VI 125/25 mcg with UMEC 125 mcg is in contrast to that reported for placebo-controlled study 361 which showed a statistically significant difference for the comparison.

In both active-comparator studies, all comparisons of UMEC/VI 62.5/25 mcg and 125/25 mcg with tiotropium for trough FEV_1 at Day 169 achieved p-values of <0.05. Improvements in trough FEV_1 for UMEC/VI 125/25 mcg compared to tiotropium were statistically significant in both studies and improvements in trough FEV_1 for UMEC/VI 62.5/25 mcg were statisticially significant in study 361 (see Section 1.6.1.3 for study 361). In study 374, the p-value is nominal for the comparison of UMEC/VI 62.5/25 mcg with tiotropium as a prior test in the predefined testing hierarchy (the comparison of UMEC/VI 125/25 mcg with UMEC 125 mcg for trough FEV_1 at Week 24) did not achieve statistical significance.

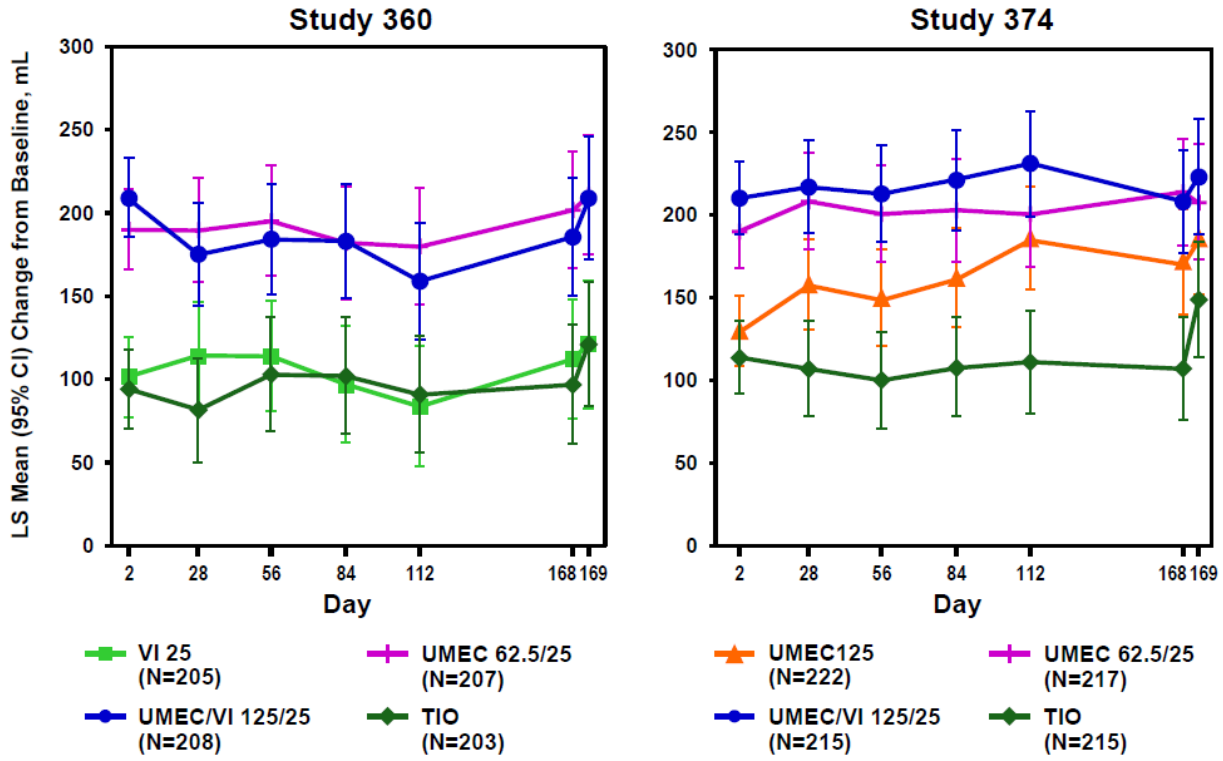
Figure 5 **LS Mean Change from Baseline for Trough FEV_1 (mL) at Day 169: (Studies 360 and 374)**



Abbreviations: FEV_1=forced expiratory volume in 1 second; LS=least squares; UMEC=umeclidinium bromide; VI=vilanterol

Throughout these studies, both doses of UMEC/VI (62.5/25 and 125/25 mcg) showed mean increases in trough FEV_1 compared with tiotropium and VI 25 mcg (Figure 6). For comparisons of UMEC/VI 125/25 mcg with UMEC 125 mcg, mean increases in trough FEV_1 were demonstrated for UMEC/VI 125/25 mcg at Day 2, 28, 56, and 84. At subsequent visits, differences between UMEC/VI 125/25 mcg and UMEC 125 mcg were not observed. Of note, an increase in the mean change from baseline for trough FEV_1 between Day 84 and Day 112 was observed in the UMEC 125 mcg group, while the increases from baseline in trough FEV_1 were generally consistent throughout the 24-week treatment period in the UMEC/VI 125/25 mcg group. The additional improvements in trough FEV_1 observed from Day 112 onwards in the UMEC 125 mcg group in this study were not evident in the UMEC 125 mcg group in study 361.

Figure 6 **LS Mean Change from Baseline for Trough FEV_1 (mL) over 24 Weeks (Studies 360 and 374)**



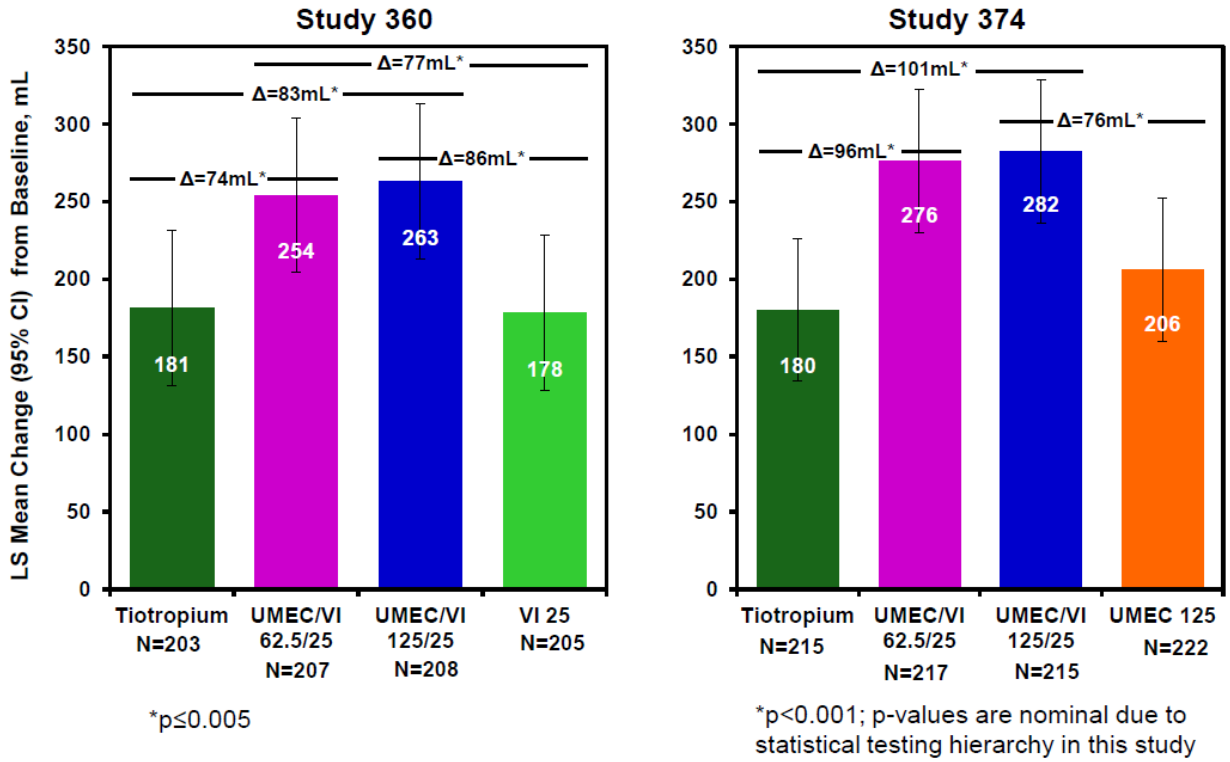
Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

In study 360, statistically significant increases in 0 to 6 hour weighted mean FEV_1 were demonstrated for comparisons of UMEC/VI 62.5/25 and 125/25 mcg with VI 25 mcg at Day 168 (Figure 7), demonstrating the contribution of UMEC to the combination. Additionally, both doses of UMEC/VI demonstrated statistically significant improvements in 0 to 6 hour weighted mean FEV_1 compared with tiotropium.

In study 374, comparisons of UMEC/VI 62.5/25 and 125/25 mcg with UMEC 125 mcg and tiotropium achieved p-values of <0.05 for 0 to 6 hour weighted mean FEV_1. However, the p-values for these comparisons were nominal as a prior test in the predefined testing hierarchy did not achieve statistical significance.

Overall, these findings demonstrate that both doses of UMEC/VI provide clinically meaningful improvements in lung function compared to VI monotherapy and compared to tiotropium, an established LAMA bronchodilator therapy for COPD.

Figure 7 LS Mean Change from Baseline for 0 to 6 hour Weighted Mean FEV_1 (mL) at Day 168 (Studies 360 and 374)



Abbreviations: FEV_1=forced expiratory volume in 1 second; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

1.6.1.4. Missing Data Sensitivity Analyses

Missing data in the Primary Efficacy Studies was mainly due to subject withdrawal; the proportion of subjects excluded from analysis due to missing covariates was small (<2% in each study). A missing value between two non-missing values was implicitly interpolated in all analyses.

Sensitivity analyses using various multiple imputation methods (discussed in the full briefing document, Section 4.2.7) were conducted and in each case the results were consistent with the primary analysis. The efficacy analyses are, therefore, considered robust to the impact of missing data.

1.6.1.5. Other Efficacy Measures

Placebo-controlled Studies

Assessment of symptomatic benefit was based on subject-reported use of rescue albuterol, shortness of breath with daily activities (SOBDA) score, and transition dyspnea index (TDI) focal score. Health-related quality of life was assessed by SGRQ score. Data on COPD exacerbations were also collected.

Consistent with the prescribing information for other long-acting bronchodilators, a description of the findings for rescue albuterol use and the SGRQ score from the placebo-controlled studies is intended to be included in the product prescribing information.

- Over the 24-week treatment period, each dose of UMEC/VI (62.5/25 and 125/25 mcg) demonstrated a statistically significant ($p<0.001$) reduction in rescue albuterol use (number of puffs per day) as compared with placebo (study 373, UMEC/VI 62.5/25 mcg: -0.8 [95% CI: -1.3,-0.3]); study 361 UMEC/VI 125/25 mcg: -1.5 [95% CI: -1.9,-1.0]).
- Improvements in SGRQ score at Week 24 were statistically significant ($p\leq0.001$) and proximate to the minimally clinically important difference (MCID) score of -4.0 units for comparisons of UMEC/VI with placebo (study 373, UMEC/VI 62.5/25 mcg: -5.51 [95% CI: -7.88,-3.13]); study 361, UMEC/VI 125/25 mcg: -3.6 [95% CI: -5.76,-1.44]).

Although not intended for US labeling, benefit for both UMEC/VI doses was also demonstrated based on clinically meaningful improvements in dyspnea compared with placebo as measured by the TDI focal score and improvements in patient-reported dyspnea with daily activities compared with placebo as measured by the Shortness of Breath with Daily Activities (SOBDA) questionnaire. Additionally, based on analysis of time to first exacerbation, both doses of UMEC/VI lower the risk of COPD exacerbation (defined as an acute worsening of symptoms of COPD requiring the use of any treatment other than study medication or rescue albuterol) compared with placebo. Supportive data for these endpoints are presented in the full briefing document.

1.6.2. Exercise/Lung Function Studies: Supportive Lung Function Efficacy

The 12-week Exercise/Lung Function Studies (studies 417 and 418) were randomized, double-blind, placebo-controlled, 2-period (12 weeks per period), incomplete block crossover studies designed to evaluate exercise endurance time (EET), lung function, and safety of once-daily UMEC/VI (125/25 mcg and 62.5/25 mcg), UMEC (125 mcg and 62.5 mcg), and VI 25 mcg in subjects with COPD.

Enrollment criteria were similar to the Primary Efficacy Studies except for an inclusion criterion for lung hyperinflation defined by a resting functional residual capacity (FRC) of ≥120% of predicted normal. This requirement was included to select subjects most likely to have exercise limitation, as hyperinflation is a significant factor in determining exercise capacity. Additionally, a lower limit was applied for post-albuterol FEV_1 (≥35% of predicted normal values) to preclude subjects with very severe disease from performing exercise tests.

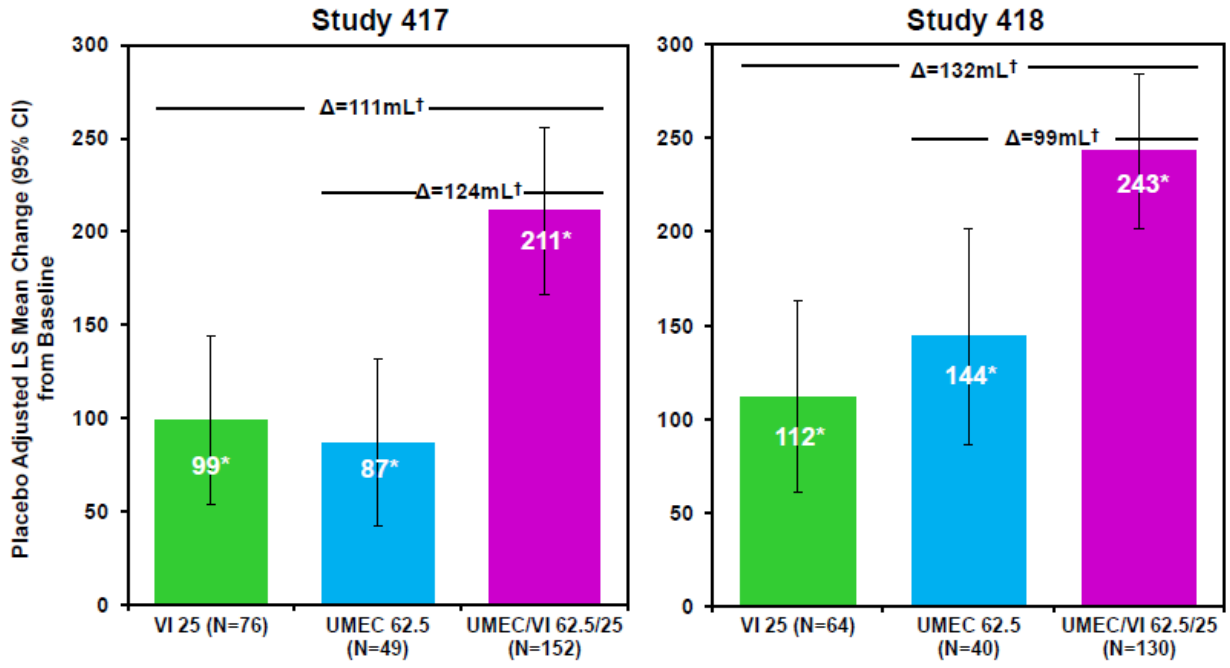
Co-primary endpoints were EET and trough FEV_1 at Week 12. Safety assessments included the reporting of AEs, routine clinical laboratory assessments, evaluation of vital signs, and 12-lead ECG measurements.

Demographic characteristics of subjects in the Exercise/Lung Function Studies were similar to those reported for the Primary Efficacy Studies. The mean post-albuterol percent predicted FEV_1 was 51.3%. Inhaled corticosteroid use was reported by 33% of subjects. The mean percent predicted normal FRC was 153.6% in study 417 and 151.6% in study 418.

The majority of subjects completed the study period(s) they started (81% to 90% across the UMEC/VI, UMEC, and VI treatments vs. 83% for placebo).

The co-primary endpoint of trough FEV_1 from these studies provide supportive evidence of lung function efficacy for both doses of UMEC/VI (62.5/25 and 125/25 mcg), for the UMEC (62.5 and 125 mcg) and VI 25 mcg monotherapies compared with placebo at Week 12, and for the contribution of each component to the efficacy of UMEC/VI 62.5/25 mcg (Figure 8).

Figure 8 Placebo-Adjusted LS Mean Change from Baseline for Trough FEV_1 (mL) at Week 12 (Studies 417 and 418)



*p≤0.003 for comparisons of UMEC/VI 62.5/25, UMEC 62.5, and VI with placebo
†p<0.001 for comparisons of UMEC/VI 62.5/25 with UMEC 62.5 and VI

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; UMEC=umeclidinium bromide; VI=vilanterol
Note: p-values are nominal for comparisons in study 417 as a result of a prior test failure in the predefined testing hierarchy

1.6.3. Summary of Trough FEV_1 Data Demonstrating the Efficacy of the UMEC 62.5 mcg and VI 25 mcg Components

Neither of the components of UMEC/VI 62.5/25 mcg is approved as a monotherapy for the treatment of COPD. Therefore, an important aspect of the clinical development program was to demonstrate the efficacy of the UMEC and VI components as compared with placebo.

Data demonstrating the efficacy of the UMEC 62.5 mcg and VI 25 mcg components are provided from the 24-week Primary Efficacy Studies (primary endpoint of trough FEV_1) and the 12-week Exercise/Lung Function Studies (co-primary endpoint of trough FEV_1) (Table 5). These data demonstrate that the doses of UMEC and VI selected for the combination product are efficacious.

Table 5 Summary of Efficacy of UMEC 62.5 mcg and VI 25 mcg for Trough FEV_1

	Time Point	Treatment Difference (mL)	95% CI	p-value
UMEC 62.5 vs. placebo				
Study 373	Day 169	115	76, 155	<0.001
Study 417	Week 12	87	30, 143	0.003 [a]
Study 418	Week 12	144	86, 203	<0.001
VI 25 vs. placebo				
Study 361	Day 169	124	86, 162	<0.001
Study 373	Day 169	72	32, 112	<0.001
Study 417	Week 12	99	50, 148	<0.001 [a]
Study 418	Week 12	112	61, 163	<0.001

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; UMEC=umeclidinium bromide; VI=vilanterol
Note: The individual Primary Efficacy Studies were powered for the comparisons presented in this table. The individual Exercise/Lung Function Studies were not powered for the comparisons presented in this table and are considered supportive of the powered comparisons.

a. p-values are nominal for this comparison according to the terms of the testing hierarchy for study 417.

1.6.4. Summary of Trough FEV_1 Data Demontrating the Contribution of UMEC 62.5 mcg and VI mcg to the Efficacy of UMEC/VI 62.5/25

As UMEC/VI is a combination product, the benefit of each component to the efficacy of the combination to improve airflow obstruction must be demonstrated.

Data demonstrating that both UMEC 62.5 mcg and VI 25 mcg contribute to the efficacy of UMEC/VI 62.5/25 mcg are provided from the 24-week Primary Efficacy Studies (primary endpoint of trough FEV_1) and the 12-week Exercise/Lung Function Studies (co-primary endpoint of trough FEV_1) (Table 6). Across these studies:

- All comparisons (across 4 studies) of UMEC 62.5/25 mcg with VI 25 mcg demonstrated improvements in trough FEV_1, confirming the contribution of UMEC 62.5 mcg to the efficacy of the combination.

- All comparisons (across 3 studies) of UMEC 62.5/25 mcg with UMEC 62.5 mcg demonstrated improvements in trough FEV_1, confirming the contribution of VI 25 mcg to the efficacy of the combination.

Table 6 Summary of Data Demonstrating the Contribution of UMEC 62.5 mcg and VI 25 mcg to the Efficacy of UMEC/VI 62.5/25 mcg for Trough FEV_1

	Time Point	Treatment Difference (mL)	95% CI	p-value
Contribution of UMEC 62.5: Comparison of UMEC/VI 62.5/25 vs. VI 25				
Study 373	Day 169	95	60, 130	<0.001
Study 360	Day 169	90	39, 142	<0.001
Study 417	Week 12	111	62, 161	<0.001 [a]
Study 418	Week 12	132	81, 183	<0.001
Contribution of VI 25: Comparison of UMEC/VI 62.5/25 vs. UMEC 62.5				
Study 373	Day 169	52	17, 87	0.004
Study 417	Week 12	124	67, 181	<0.001 [a]
Study 418	Week 12	99	41, 157	<0.001

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; UMEC=umeclidinium bromide; VI=vilanterol
Note: The individual Primary Efficacy Studies were powered for the comparisons presented in this table. The individual Exercise/Lung Function Studies were not powered for the comparisons presented in this table and are considered supportive of the powered comparisons.
a. p-values are nominal for this comparison according to the terms of the testing hierarchy for study 417.

1.7. Summary of Clinical Safety Results

The safety of UMEC/VI, UMEC, and VI in COPD was evaluated from a comprehensive database which included a total of 14 clinical studies with treatment periods of at least 4 weeks and a relevant UMEC/VI, UMEC or VI treatment arm (All COPD Studies Grouping). Key features of these studies are tabulated in Appendix 10.4.

Integrated data from the four 24-week Primary Efficacy Studies provide safety data for UMEC/VI and UMEC and VI monotherapies and underpin the safety conclusions supporting the use of UMEC/VI in the treatment of COPD. Data on the long-term safety of UMEC and UMEC/VI are provided from the 52-week Long-term Safety Study which evaluated the 125 mcg dose of UMEC and the 125/25 mcg dose of UMEC/ VI.

Long-term safety data for VI 25 mcg were reviewed as part of the BREO ELLIPTA NDA submission which has been approved by the FDA. These data are not presented in this briefing document.

An external blinded independent adjudication committee evaluated all deaths and nonfatal serious adverse reports (SARs) from the 7 Phase III studies in the UMEC/VI COPD clinical development program and a further Phase III study with UMEC monotherapy, each of which included treatment periods of at least 12 weeks duration and a UMEC/VI or UMEC treatment group:

- 4 Primary Efficacy Studies,
- 2 Exercise/Lung Function Studies
- Long-term Safety Study, and
- Study 408

Fatal events were categorized as respiratory, cardiovascular (CV), cancer, other cause of death, or unknown. Nonfatal events were categorized as respiratory, CV, other, or unknown. See Appendix 10.5 for a description of the adjudication process. The adjudication subcategories may not correspond to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) or adverse event of special interest (AESI) subcategories which are comprised of events in selected MedDRA Standard MedDRA Queries (SMQs) and/or individual PTs. For this reason, an event adjudicated by the committee may fall under a different category than that reported by the investigator.

Because CV effects have been associated with both classes of long-acting bronchodilators, a comprehensive evaluation of potential CV risk was undertaken. This included an analysis of Major Adverse Cardiac Event (MACE) (using integrated data from the studies included in the adjudication process) and an evaluation of Cardiovascular AESIs. Additionally, extensive cardiac monitoring with ECG and Holter ECGs was performed for the Primary Efficacy Studies and the Long-term Safety Study.

Specific pharmacologic LAMA and LABA class effects were assessed in all Phase III studies in the UMEC/VI COPD clinical development program through an evaluation of certain pre-specified AESIs. In addition, as pneumonia and lower respiratory tract infections (LRTIs) are commonly reported in patients with COPD, these events were also assessed in the UMEC/VI COPD program. Data on the occurrence of AESIs are reported for the Primary Efficacy Studies and Long-term Safety Study as these studies form the majority of the safety database.

1.7.1. Extent of Exposure

A total of 8138 subjects received at least one dose of study medication; approximately 6000 subjects received UMEC/VI, UMEC, or VI with approximately 2500 receiving UMEC/VI. The total patient-years of exposure to UMEC/VI is approximately 980. The number of subjects exposed to study medication and included in safety evaluations is consistent with International Conference on Harmonisation (ICH) E1 guidance [ICH E1].

In the 24-week Primary Efficacy Studies, 1389 subjects were exposed to UMEC/VI for at least 20 weeks. Greater than 48 weeks exposure to the UMEC 125/25 mcg (N=146) and UMEC 125 mcg (N=133) in the 52-week Long-term Safety Study support the evaluation of long-term safety for the UMEC/VI 62.5/25 mcg and UMEC 62.5 mcg doses.

1.7.2. Demographic and Baseline Characteristics

The demographic and baseline characteristics of patients in the Primary Efficacy Studies are described in Section 1.6.1.2.

The demographic and baseline characteristics of subjects in the Long-term Safety Study were similar to the Primary Efficacy Studies. The mean age was 61.3 years and more males (67%) than females were enrolled. The predominant race category was White (94%). More than half (63%) of the subjects were current smokers and approximately one third (34%) were using concurrent ICS therapy. The mean post-albuterol percent predicted FEV_1 was 54.7%. The majority of subjects (68%) did not report a COPD exacerbation requiring oral corticosteroids or antibiotics in the year prior to screening.

The COPD population as a whole commonly experience CV co-morbidities [Curkendall, 2006]. In the Primary Efficacy Studies and the Long-term Safety Study, the majority of subjects (55-68% in each treatment group) reported at least one CV risk factor (e.g., hypertension [46-59%] hyperlipidemia [23-28%] or diabetes [10-15%]) and 18-35% reported a current cardiac disorder. The majority of subjects (51-61%) in each treatment group in these studies also reported taking at least one CV medication, including antihypertensive medications and cholesterol-lowering agents. There were no specific exclusionary criteria regarding CV risk in the UMEC/VI Phase III studies other than exclusion for clinically significant uncontrolled CV disease based on the medical judgment of the study investigator and/or an abnormal and clinically significant ECG finding.

1.7.3. Deaths

Given a relatively older population with comorbidities, deaths are expected in a COPD program. A total of 46 deaths were reported across All COPD studies (N=8138) with 22 deaths reported in the Primary Efficacy Studies and 5 deaths in the Long-term Safety Study.

In the Primary Efficacy Studies, 5 deaths were reported in the UMEC/VI 62.5/25 group and 1 death in the UMEC/VI 125/25 group compared to 3 deaths in the placebo group. Overall,the incidence of fatal events was low in the Primary Efficacy Studies (<1% in each treatment group).

No treatment or dose-related pattern was identified either overall or by adjucticated category (CV, respiratory, cancer, other, and unknown) (Table 7). The distribution by category is consistent with the disease population and comorbid conditions.

Table 7 Adjudicated Fatal Adverse Serious Adverse Reports (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

Fatal Serious Adverse Report Category Subcategory (Where Applicable)	Number (%) of Subjects Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Any fatal serious adverse report	3 (<1)	5 (<1)	1 (<1)	3 (<1)	2 (<1)	6 (<1)	2 (<1)
Cardiovascular – any type	1 (<1)	2 (<1)	0	0	0	2 (<1)	0
Sudden death	1 (<1)	1 (<1)	0	0	0	0	0
Myocardial infarction/ischemic heart disease	0	0	0	0	0	1 (<1)	0
Congestive heart failure	0	0	0	0	0	1 (<1)	0
Stroke – haemorrhagic	0	1 (<1)	0	0	0	0	0
Respiratory – any type	1 (<1)	2 (<1)	0	1 (<1)	0	1 (<1)	0
COPD exacerbation without evidence of pneumonia	1 (<1)	2 (<1)	0	1 (<1)	0	1 (<1)	0
Cancer – any type	0	0	0	0	2 (<1)	1 (<1)	0
Lung cancer	0	0	0	0	1 (<1)	0	0
Unknown primary	0	0	0	0	0	1 (<1)	0
Other cancer cause	0	0	0	0	1 (<1)	0	0
Other – any type	0	0	1 (<1)	1 (<1)	0	0	1 (<1)
Unknown – any type	1 (<1)	1 (<1)	0	1 (<1)	0	2 (<1)	1 (<1)
Inadequate information	1 (<1)	1 (<1)	0	1 (<1)	0	0	0
Indeterminate	0	0	0	0	0	2 (<1)	1 (<1)

Abbreviations: COPD=chronic obstructive pulmonary disease; MedDRA=Medical Dictionary for Regulatory Activities: PT=preferred term: SMQ=standard MedDRA query; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

In the Long-term Safety Study, there were no deaths in the UMEC 125/25 mcg treatment group. The mortality incidence was 2% (4 subjects) in the UMEC 125 mcg treatment group and <1% (1 subject) in the placebo treatment group (Table 8). The higher number of fatal events occurring in the UMEC 125 mcg treatment group was driven mainly by 3 deaths which were oncologic in nature. There was no pattern to the reported types of cancer (metastases to spine [duration of UMEC exposure: 5 months], metastases to liver [duration of UMEC exposure: 4 days], and mediastinal neoplasm [duration of UMEC exposure: 1 year]) in the UMEC group.

Table 8 Adjudicated Fatal Serious Adverse Reports (Study 359)

Fatal Serious Adverse Report Category Subcategory (Where Applicable)	Number (%) of Subjects Placebo N=109	 UMEC/VI 125/25 N=226	 UMEC 125 N=227
Any type	1 (<1)	0	4 (2)
Cardiovascular – any type	1 (<1)	0	1 (<1)
Myocardial infarction/ischemic heart disease	1 (<1)	0	0
Congestive heart failure	0	0	1 (<1)
Respiratory – any type	0	0	1 (<1)
COPD exacerbation with evidence of pneumonia	0	0	1 (<1)
Cancer – any type	0	0	3 (1)
Unknown primary	0	0	3 (1)
Other – any type	0	0	0
Unknown – any type	0	0	0

Abbreviations: AESI=adverse event of special interest; COPD=chronic obstructive pulmonary disease; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term: SMQ=standard MedDRA query; UMEC=umeclidinium bromide VI=vilanterol

Note: One death in the UMEC 125 mcg group was reported in both the respiratory and cancer categories.

1.7.4. Non-fatal Adjudicated Serious Adverse Reports

In the Primary Efficacy Studies, the incidence of nonfatal on-treatment SARs was 5% to 6% across all treatment groups including placebo and tiotropium. Similarly, in the Long-term Safety Study, the incidence of nonfatal on-treatment SAR was comparable across treatment groups (UMEC/VI 125/25 mcg: 6%; UMEC 125 mcg: 7%; placebo: 6%).

No treatment or dose-related patterns were identified for adjudicated nonfatal SARs, either overall or by adjudicated category in either study grouping.

1.7.5. AEs Leading to Withdrawal or Permanent Discontinuation of Study Drug

In the Primary Efficacy Studies, the incidence of AEs leading to withdrawal or permanent discontinuation of study drug (including on-treatment and post-treatment fatal, serious, and non-serious AEs) was low (5% to 7% in all treatment groups including placebo and tiotropium) and no pattern was discernible in the types of AEs that led to withdrawal or permanent discontinuation of study drug. In the Long-Term Safety Study, the incidence of on-treatment AEs leading to permanent discontinuation of study drug or withdrawal (including on-treatment and post-treatment fatal, serious, and non-serious AEs) was 9% for the UMEC 125 mcg treatment group, 8% for the UMEC/VI 125/25 mcg treatment group, and 11% for placebo. The incidences of individual AEs leading to permanent discontinuation of study drug or withdrawal in the UMEC 125/25 mcg treatment group were the same as or less than that reported for placebo. The UMEC 125 mcg treatment group had a slightly higher incidence of AEs leading to withdrawal of ventricular extrasystoles (2%), supraventricular tachycardia (SVT) (1%), and sinus tachycardia (1%) compared with placebo (<1% for each event), however, this same pattern was not observed in the UMEC/VI 125/25 mcg treatment group.

1.7.6. Cardiovascular Adverse Events of Special Interest

The evaluation of CV AESIs defined a priori for UMEC and/or VI, included acquired long QT interval, cardiac arrhythmias, cardiac failure, cardiac ischaemia, hypertension, sudden death, and stroke. The AE terms included in these evaluations were based on standardized and commonly used selections (i.e. MedDRA SMQs), which are not necessarily diagnostic but were chosen to assure that AE terms that may be associated with the safety concern of interest were included.

Overall, no dose- or treatment-related patterns were identified in the incidence of AEs in CV AESI categories in the Primary Efficacy Studies (Table 9) or the Long-term Safety Study (Table 10). The most commonly reported CV AESI category in both study groupings was cardiac arrhythmias followed by hypertension.

There was a low incidence of AEs in the cardiac arrhythmia AESI category in either the Primary Efficacy Studies or the Long-term Safety Study. A higher number of subjects had reports of supraventricular tachyarrhythmias (e.g. atrial fibrillation, atrial flutter, sinus tachycardia, and supraventricular extrasystoles) in the active treatment groups compared with placebo (see Section 5.4.3 in the full briefing document).

Table 9 Cardiovascular Special Interest Subgroup: On-treatment AESIs (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

Cardiovascular AESI Category	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Incidence	Number (%) of Subjects						
Any Cardiovascular AESI	40 (7)	70 (8)	55 (7)	41 (10)	52 (8)	95 (9)	27(6)
Acquired long QT	0	0	2 (<1)	1 (<1)	0	0	0
Cardiac arrhythmias	18 (3)	24 (3)	19 (2)	20 (5)	20 (3)	46 (4)	9 (2)
Cardiac failure	6 (1)	11 (1)	11 (1)	7 (2)	7 (1)	12 (1)	5 (1)
Cardiac ischaemia	5 (<1)	11 (1)	12 (1)	7 (2)	5 (<1)	12 (1)	4 (<1)
Hypertension	11 (2)	25 (3)	17 (2)	12 (3)	21 (3)	29 (3)	11 (3)
Sudden death	0	0	0	0	0	1 (<1)	0
Stroke	2 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (<1)	1 (<1)

Abbreviations: AESI=adverse event of special interest; SY=subject-years; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Table 10 Cardiovascular Special Interest Subgroup: On-treatment AESIs (Study 359)

Cardiovascular AESI Category	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Incidence	Number (%) of Subjects		
Any Cardiovascular AESI	25 (23)	34 (15)	49 (22)
Acquired long QT	0	0	0
Cardiac arrhythmias	17 (16)	26 (12)	39 (17)
Cardiac failure	1 (<1)	2 (<1)	4 (2)
Cardiac ischaemia	4 (4)	4 (2)	4 (2)
Hypertension	7 (6)	8 (4)	6 (3)
Sudden death	0	0	0
Stroke	0	0	1 (<1)

Abbreviations: AESI=adverse events of special interest; SY=subject-years; UMEC=umeclidinium bromide; VI=vilanterol

1.7.7. MACE

The MACE evaluation was performed using integrated data from the 8 UMEC/VI Phase III studies included in the adjudication process.

The MACE events included in the planned analysis (broad analysis) were defined a priori as follows:

- Adjudicated CV deaths,
- Cardiac Ischaemia Special Interest AE Subgroup (broad array of AE terms; Myocardial Infarction standard MedDRA query (SMQ) and Other Ischaemic Heart Disease SMQ) excluding fatalities, and
- Stroke Special Interest AE Subgroup (Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ) excluding fatalities.

A more focused post-hoc MACE analysis (narrow analysis) was conducted which included adjudicated CV death and stroke, as described for the planned analysis, but did not include the broad array of terms specified for the cardiac ischaemic special interest subgroup in the planned analysis. Only events relating specifically to myocardial infarction (defined as the PTs of "myocardial infarction" and "acute myocardial infarction" and described as "myocardial infarction" events) were included.

For both the broad and narrow analyses, no evidence for an increase in MACE with UMEC/VI or the individual components compared with placebo was seen (Table 11). Total MACE were equal to or less than that reported for placebo for all active treatments. The incidences of adjudicated CV deaths and nonfatal stroke were low and similar across all treatment groups including placebo.

For the broad MACE analysis, the incidence of nonfatal cardiac ischaemia AESI (Myocardial infarction SMQ and Other ischaemic heart disease SMQ) and exposure-adjusted frequency of subjects with events were similar across treatment groups and no dose- or treatment-related patterns were identified.

For the narrow MACE analysis, the incidence of non-fatal myocardial infarction (MedDRA PTs of myocardial infarction and acute myocardial infarction) was low (<1%) across all treatment groups, although small imbalances in exposure-adjusted frequency were observed between UMEC- and VI-containing treatment groups when compared with placebo and tiotropium. There was no obvious dose relationship or additive effect from the combination. Whether this represents a true effect is difficult to determine due to the small numbers.

Table 11 Major Adverse Cardiac Events: Broad and Narrow Analyses (Integrated Studies 361, 373, 360, 374, 417, 418, 359, and 408)

	Placebo N=1053 SY=369	UMEC/VI 62.5/25 N=1124 SY=408	UMEC/VI 125/25 N=1330 SY=573	UMEC 62.5 N=576 SY=202	UMEC 125 N=1016 SY=449	VI 25 N=1174 SY=441	TIO N=423 SY=173
Incidence	Number (%) of Subjects						
MACE composite (broad)	20 (2)	15 (1)	22 (2)	9 (2)	14 (1)	17 (1)	6 (1)
MACE composite (narrow)	7 (<1)	5 (<1)	6 (<1)	2 (<1)	7 (<1)	8 (<1)	1 (<1)
Cardiovascular death [a] (broad and narrow)	2 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)	0
Nonfatal stroke AESI [b] (broad and narrow)	4 (<1)	0	3 (<1)	1 (<1)	2 (<1)	4 (<1)	1 (<1)
Nonfatal cardiac ischaemia AESI [c] (broad)	14 (1)	13 (1)	19 (1)	8 (1)	11 (1)	12 (1)	5 (1)
Nonfatal myocardial infarction [d] (narrow)	1 (<1)	3 (<1)	3 (<1)	1 (<1)	4 (<1)	2 (<1)	0
Exposure-adjusted frequencies	Number of Subjects with Events per 1000 Subject-Years						
MACE composite (broad)	54.3	36.8	38.4	44.5	31.2	38.5	34.7
MACE composite (narrow)	19.0	12.3	10.5	9.9	15.6	18.1	5.8
Cardiovascular death [a] (broad and narrow)	5.4	4.9	0	0	2.2	4.5	0
Nonfatal stroke AESI [b] (broad and narrow)	10.9	0	5.2	4.9	4.5	9.1	5.8
Nonfatal cardiac ischaemia AESI [c] (broad)	38.0	31.9	33.2	39.5	24.5	27.2	28.9
Nonfatal myocardial infarction [d] (narrow)	2.7	7.4	5.2	4.9	8.9	4.5	0
Total MACE	Total Number of Events						
Total MACE, n (broad)	22	16	22	11	15	18	6
Total MACE, n (narrow)	8	5	6	2	7	8	1

Abbreviations: AESI=adverse event of special interest; ECG=electrocardiogram; MACE=major adverse cardiac event; MedDRA= Medical Dictionary for Regulatory Activities; SMQ=standard MedDRA query; SY=subject-years; PT=preferred term; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: The broad analysis was a priori and the narrow analysis was post-hoc.

a. Cardiovascular deaths were independently adjudicated (see Appendix 10.5).
b. The following MedDRA SMQ contributed to the nonfatal stroke AESI category: Central nervous system haemorrhages and cerebrovascular conditions SMQ.
c. The following MedDRA SMQs contributed to the cardiac ischaemia AESI category: Myocardial Infarction SMQ; Other Ischaemic Heart Disease SMQ.
d. The following MedDRA PTs contributed to myocardial infarction: myocardial infarction and acute myocardial infarction.

1.7.8. Cardiac Monitoring

Other cardiac safety parameters assessed in the program included serial ECGs and Holter monitoring and in addition a Thorough QT study was conducted. ECGs were collected from approximately 4700 subjects in the Primary Efficacy Studies and from approximately 560 subjects in the Long-term Safety Study. Twenty-four hour Holter ECGs were collected from approximately 390 subjects in the two placebo-controlled Primary Efficacy Studies and from

approximately 490 subjects in the Long-term Safety Study. In addition, a Thorough QT study was performed in healthy volunteers

In summary, for the Primary Efficacy and Long-term Safety studies:

- A higher incidence of post-baseline ECG abnormalities from abnormal clinically significant ECGs of atrial fibrillation, atrial fibrillation with rapid response [rate >100 bpm], or SVT were noted in the active treatment groups compared with placebo (Table 12).
- There were few findings of atrial arrhythmias on post-baseline abnormal clinically significant Holter ECGs of atrial fibrillation, atrial fibrillation with rapid response (rate >100bpm), or sustained SVT (>100bpm, >30beats) in either the two placebo-controlled Primary Efficacy Studies or the Long-term Safety Study. In the Long-term Safety Study, a higher incidence of sustained SVT (>100 bpm, >30 beats) findings were noted in the UMEC 125 mcg (5%) compared with placebo (2%) (Table 13).
- ECG and Holter findings of ventricular arrhythmias were similar to placebo in both the Primary Efficacy Studies and the Long-term Safety Study (see Section 5.4.4.1).
- There were no clinically relevant changes in QT interval, PR interval or HR on ECGs (see Section 5.4.4.1).

Table 12 Selected Atrial Arrhythmia ECG Findings from All Subjects with Any Abnormal Clinically Significant ECG Interpretation (Integrated Primary Efficacy Studies 361, 373, 360, and 374 and Study 359)

	Number (%) of Subjects						
Primary Efficacy Studies	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Post-baseline atrial arrhythmias							
n	555	842	832	417	629	1034	423
Atrial fibrillation (<100bpm)	1 (<1)	3 (<1)	8 (<1)	3 (<1)	2 (<1)	7 (<1)	1 (<1)
Atrial fibrillation with rapid ventricular response (rate >100bpm)	0	3 (<1)	2 (<1)	2 (<1)	3 (<1)	7 (<1)	2 (<1)
Supraventricular tachycardia (>100/min)	0	1 (<1)	1 (<1)	0	2 (<1)	2 (<1)	2 (<1)
Study 359	Placebo N=109		UMEC/VI 125/25 N=226		UMEC 125 N=227		
Post-baseline - atrial arrhythmias							
n	109		226		227		
Atrial fibrillation (<100bpm)	0		1 (<1)		1 (<1)		
Atrial fibrillation with rapid ventricular response (rate >100bpm)	0		1 (<1)		2 (<1)		
Supraventricular tachycardia (>100/min)	0		0		0		

Abbreviations: ECG=electrocardiogram; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Table 13 Selected Atrial Arrhythmia Holter ECG Findings from All Subjects with Any Abnormal Clinically Significant Holter ECG Abnormality (Integrated Studies 361 and 373 [TFH Subset] and Study 359)

	Number (%) of Subjects					
Primary Efficacy Studies	Placebo N=73	UMEC/VI 62.5/25 N=53	UMEC/VI 125/25 N=55	UMEC 62.5 N=54	UMEC 125 N=53	VI 25 N=108
Post-randomization atrial arrhythmias						
n	72	53	55	54	53	107
Atrial fibrillation	0	0	0	0	0	0
Atrial fibrillation with rapid ventricular response (rate >100bpm)	0	0	1 (2)	1 (2)	0	1 (<1)
Sustained supraventricular tachycardia (>100bpm, >30beats)	1 (1)	1 (2)	0	2 (4)	0	3 (3)
Study 359	Placebo N=109		UMEC/VI 125/25 N=226		UMEC 125 N=227	
Post-randomization atrial arrhythmias						
n	90		206		198	
Atrial fibrillation	0		0		0	
Atrial fibrillation with rapid ventricular response (rate >100bpm)	2 (2)		1 (<1)		3 (2)	
Sustained supraventricular tachycardia (>100bpm, >30beats)	2 (2)		5 (2)		9 (5)	

Abbreviations: ECG=electrocardiogram; TFH=twenty-four hour; UMEC=umeclidinium bromide; VI=vilanterol.

More detailed presentations of arrhythmia findings are provided in Section 5.4.3 and 5.4.4.

In a thorough QT trial in healthy volunteers, there was no evidence of a clinically relevant effect on QT interval corrected for heart rate by Fridericia's formula (QTc[F]) following UMEC/VI 125/25 mcg, representing twice the UMEC dose in the proposed therapeutic UMEC/VI dose, or UMEC 500 mcg. For a supratherapeutic dose of UMEC/VI 500/100 mcg, the upper bound of the 90% confidence interval (CI) (10.2 msec) for change from baseline at 30 min after dosing superseded the 10 msec threshold. This was the only time point where the upper 90% CI exceeded 10 msec.

1.7.9. Non-Cardiovascular Adverse Events of Special Interest

There were no significant findings with regard to non-CV AEs by special interest groups (effects on glucose or potassium, tremor, urinary retention, ocular effects, gallbladder disorders, intestinal obstruction, and anticholinergic effects) or LRTI and pneumonia, and no evidence of treatment- or dose-related effects for these events in either the Primary Efficacy Studies or the Long-term Safety Study.

1.7.10. Frequently Reported AEs

The overall incidence of AEs in the Primary Efficacy Studies was similar across all active treatment groups (50% to 55%) and the placebo and tiotropium groups (48% and 49%, respectively) (Table 14). No noteworthy differences across treatment groups were observed in

the incidence of individual AEs reported by ≥3% of subjects in any treatment group. The most frequently reported AEs were those commonly experienced in the general COPD population.

Table 14 Summary of On-treatment Adverse Events Reported by 3% or More of Subjects Within Either UMEC/VI Treatment Group (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

	Number (%) of Subjects						
Preferred Term	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Any AE	264 (48)	447 (53)	438 (53)	216 (52)	348 (55)	518 (50)	208 (49)
Headache	58 (10)	76 (9)	75 (9)	32 (8)	62 (10)	87 (8)	24 (6)
Nasopharyngitis	48 (9)	74 (9)	77 (9)	29 (7)	43 (7)	98 (9)	33 (8)
Cough	23 (4)	18 (2)	44 (5)	16 (4)	29 (5)	37 (4)	11 (3)
URTI	21 (4)	27 (3)	24 (3)	21 (5)	23 (4)	32 (3)	22 (5)
Back pain	20 (4)	31 (4)	23 (3)	8 (2)	27 (4)	20 (2)	15 (4)

Abbreviations: AE=adverse event; COPD=chronic obstructive pulmonary disease; TIO=tiotropium; UMEC=umeclidinium bromide; URTI=upper respiratory tract infection; VI=vilanterol

In the Long-term Safety study, the overall incidence of AEs was 53% and 58% for the UMEC/VI 125/25 mcg and UMEC 125 mcg treatment groups, respectively, compared with 52% for placebo (Table 15).

Table 15 Summary of On-treatment Adverse Events Reported by 3% or More of Subjects in the UMEC/VI Treatment Group (Study 359)

	Number (%) of Subjects		
Preferred Term	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Any AE	57 (52)	120 (53)	132 (58)
Headache	9 (8)	20 (9)	25 (11)
Nasopharyngitis	5 (5)	11 (5)	20 (9)
Ventricular extrasystoles	5 (5)	11 (5)	12 (5)
Extrasystoles	4 (4)	10 (4)	10 (4)
Back pain	3 (3)	10 (4)	9 (4)
Hypertension	5 (5)	8 (4)	4 (2)
Sinusitis	3 (3)	8 (4)	6 (3)
Influenza	5 (5)	6 (3)	5 (2)
Cough	1 (<1)	6 (3)	6 (3)

Abbreviations: AE=adverse event; UMEC=umeclidinium bromide; VI=vilanterol

1.8. Benefit/Risk

The UMEC/VI development program has demonstrated that UMEC/VI 62.5/25 mcg provides clinically relevant efficacy, as defined by measures of lung function over 24 weeks of treatment, as compared with placebo, the individual monotherapies and tiotropium in a broad range of subjects with COPD. The contribution of each component of UMEC/VI 62.5/25 mcg is supported by the superiority of the UMEC/VI combination over UMEC 62.5 mcg or VI 25 mcg

as monotherapy in measures of lung function. Though neither UMEC 62.5 mcg nor VI 25 mcg is currently approved, both were shown to be efficacious compared with placebo and to have a duration of action that supports once-daily administration. In addition to efficacy on lung function, UMEC/VI 62.5/25 mcg reduced rescue medication use, improved health-related quality of life (based on SGRQ), and improved symptoms of dyspnea as measured by TDI and SOBDA scores compared with placebo thereby providing additional evidence of beneficial effect.

UMEC/VI was well tolerated with a similar rate of AEs across all treatment groups including placebo and no significant safety concerns. No difference in the safety profile was observed between the 2 doses of UMEC/VI. Potential pharmacology-related effects such as atrial arrhythmias were observed at a low incidence with UMEC/VI treatment groups that was slightly higher than with placebo. Non-fatal myocardial infarction was also reported at a low incidence across all treatment groups. Small imbalances in exposure-adjusted frequency of non-fatal myocardial infarction between UMEC/VI treatment groups when compared with placebo were observed. There was no dose relationship or additive effect from the combination. Whether this represents a true effect on myocardial infarction is difficult to determine due to the small number of events.

The benefits of UMEC/VI 62.5/25 include improved pulmonary function, symptoms, and health-related quality of life. The overall safety profile shows a low incidence of pharmacologically predicted AEs and the data demonstrate no evidence of an increased risk with UMEC/VI over the individual components, supporting the overall conclusion of a positive benefit-risk balance for UMEC/VI 62.5/25 mcg as a maintenance bronchodilator treatment for COPD.

1.9. Overall Conclusion

UMEC/VI 62.5/25 mcg will provide a new treatment to optimize maintenance bronchodilator therapy over LAMA or LABA monotherapy with sustained efficacy over 24 hours. The safety and tolerability profile of UMEC/VI has been well characterized with no significant safety findings. UMEC/VI 62.5/25 mcg will be a safe and effective treatment available for patients who suffer from COPD.

2. INTRODUCTION

2.1. Background and Product Rationale

Chronic obstructive pulmonary disease is a preventable and treatable respiratory disease characterized by persistent airflow limitation that is a major cause of poor health, resulting in millions of deaths annually worldwide [GOLD, 2013] and contributing significantly to health care costs and morbidity [Chapman, 2006; Lopez, 2006]. As of 2012 reports, COPD was the third leading cause of death in the US [Murphy, 2012; Kosacz, 2012], resulting in 130,000 deaths every year [Murphy, 2012].

Bronchodilator medications are the mainstay of pharmacologic therapy for COPD to improve airflow obstruction and they are commonly used on a regular basis to improve symptoms, exercise limitation, and health status [GOLD, 2013]. The predominant classes of inhaled bronchodilators are muscarinic receptor antagonists and beta$_2$-agonists. Long-acting muscarinic antagonists and long-acting beta$_2$-agonists are recommended over short-acting bronchodilators for the maintenance treatment of patients with moderate to very severe disease as they are more efficacious and convenient to use [Celli, 2004; GOLD, 2013].

Combinations of the short-acting beta$_2$-agonist albuterol and the short-acting anticholinergic ipratropium (i.e., Combivent and DuoNeb) are widely used for the treatment of airflow obstruction associated with COPD. However, they are limited by frequent dosing (i.e., up to 4 times per day). There are no fixed-dose LAMA/LABA combination products currently approved in the US. A fixed-dose combination could potentially optimize bronchodilation over long-acting bronchodilator monotherapy while providing a comparable safety profile and avoiding the risk of side effects associated with increasing the dose of a single bronchodilator [GOLD, 2013].

The distinct and complementary mechanisms of action through which muscarinic antagonists and beta$_2$-agonists act to relax airway smooth muscle and improve airflow obstruction provide a scientific rationale for development of a fixed-dose LAMA/LABA combination product. Muscarinic receptor antagonists act by inhibiting the binding of acetylcholine with muscarinic receptors on airway smooth muscle, thereby inhibiting bronchoconstriction. Conversely, beta$_2$-agonists directly activate beta$_2$-adrenoreceptors on airway smooth muscle, causing smooth muscle relaxation.

The scientific rationale for a fixed-dose LAMA/LABA combination product is supported by numerous clinical studies that have confirmed the lung function benefits of long-acting bronchodilator combination therapy compared to a single long-acting bronchodilator alone (Table 16).

Table 16 Proof of Concept for LAMA/LABA Combination Therapy

Free combination	Duration	Reference	Results
tiotropium QD + formoterol BID	24 weeks	Vogelmeier, 2008	Improvement in FEV_1 2 h post-dose after 24 weeks with combination: 70mL vs. formoterol alone ($p = 0.044$)
tiotropium QD + indacaterol QD	12 weeks	Mahler, 2012	Greater increase in trough FEV_1 from baseline with combination: 70–80 mL difference vs tiotropium alone ($p < 0.001$)
tiotropium QD + formoterol BID	12 weeks	Tashkin, 2009	Greater improvement in FEV_1 AUC_{0-4} from baseline with combination (0.34 L) vs. tiotropium alone (0.17 L); $p < 0.001$
tiotropium QD + salmeterol BID	6 weeks	Van Noord, 2010	Improved average FEV_1 (0–24 h) with combination (0.142 L) vs. monotherapy with either tiotropium (0.07 L) or salmeterol (0.045 L); $p < 0.0001$
tiotropium QD + arformoterol BID	2 weeks	Tashkin, 2013	Greater improvement in FEV_1 AUC_{0-24} from baseline with combination (0.22 L) vs. monotherapy with either arformoterol (0.10 L) or tiotropium (0.08 L); $p < 0.001$

Adapted from Tashkin, 2013
Abbreviations: AUC=area under the curve; BID=twice-daily; FEV_1=forced expiratory volume in one second; LABA=long-acting $beta_2$-agonist; LAMA=long-acting muscarinic antagonist; QD=once-daily

These studies showed that the safety profile of the combinations was similar to that of the long-acting bronchodilator monotherapies. These and other clinical findings showing a positive benefit-risk profile for LAMA/LABA therapy are embodied by evidence-based guidelines on COPD disease management which recommend an incremental approach to the pharmacologic disease management, involving the use of combinations of drug classes with different or complementary mechanisms of action, and regular treatment with 1 or more long-acting bronchodilators as disease progresses [Celli, 2004; GOLD, 2013].

Thus, the development of a fixed-dose LAMA/LABA combination is based on a sound scientific and clinical rationale aimed to optimize bronchodilator response. Additionally, a once-daily combination may offer improved convenience and compliance over the use of single long-acting bronchodilators from separate inhalers.

Umeclidinium bromide/vilanterol inhalation powder (ANORO ELLIPTA) is a new fixed-dose LAMA/LABA combination product delivered orally via DPI with a 24-hour duration of action that allows for once-daily administration. ANORO ELLIPTA is the first combination product including a LAMA and a LABA component to be considered for the treatment of COPD by the FDA.

The LAMA component, UMEC, is a new molecular entity. A NDA (205382) for UMEC inhalation powder (monotherapy) was submitted to the FDA on 30 April 2013. LAMAs currently marketed for treatment of COPD in the US are Spiriva HandiHaler (tiotropium) and Tudorza Pressair (aclidinium).

Vilanterol trifenatate (VI) is a LABA and is a component of the ICS/LABA combination product containing FF and VI (BREO ELLIPTA [fluticasone furoate/vilanterol inhalation powder]).

BREO ELLIPTA received approval by the FDA for the treatment of COPD on 10 May 2013. Vilanterol is not currently approved for marketing as a monotherapy. LABAs currently approved in the US for treatment of COPD include SEREVENT ™DISKUS™ (salmeterol), Foradil Aerolizer, Performist (formoterol) (both dosed twice daily) and Arcapta Neohaler (indacaterol) (dosed once daily).

GlaxoSmithKline has completed a clinical development program supporting the inhaled UMEC/VI combination as a maintenance treatment for COPD patients, with benefit demonstrated over the component bronchodilator monotherapies (UMEC and VI) as well as tiotropium. The results of the clinical development program are described in this briefing document.

2.2. Product Description

UMEC/VI Inhalation Powder is delivered via a novel, single-step activation, multi-dose DPI for oral inhalation, ELLIPTA (Figure 9). Two, double-foil, laminate, blister strips each containing 30 blisters are contained within the inhaler to provide a total of 30 doses of UMEC/VI. One strip contains a blend of micronized UMEC with magnesium stearate and lactose as excipients. The second strip contains a blend of micronized VI with magnesium stearate and lactose as excipients. When actuated, the ELLIPTA inhaler simultaneously delivers the contents of a single blister from each of the 2 blister strips. The drug product used in the Phase III UMEC/VI clinical development program was representative of the to-be-marketed product in terms of formulation and inhaler (ELLIPTA).

Figure 9 ANORO ELLIPTA: 62.5/25 mcg Dose

The in vitro pharmaceutical performance of the product has been extensively characterized and showed that the ELLIPTA delivers consistent doses within the respirable range over the lifetime of the product.

2.3. Proposed Indication and Label Claims

ANORO ELLIPTA is indicated for the long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema.

Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

The recommended dose is 1 inhalation of ANORO ELLIPTA 62.5/25 mcg once daily.

Consistent with other approved LAMA and LABA medications, supportive findings for efficacy-related measures of rescue albuterol use for breakthrough symptoms and health-related quality of life using the SGRQ are proposed for inclusion in the Clinical Trials section of the prescribing information.

Other COPD medications such as ADVAIR™ DISKUS™ (fluticasone propionate/salmeterol inhalation powder) and Spiriva HandiHaler (tiotropium) are indicated to reduce COPD exacerbations. This claim is not sought for ANORO ELLIPTA in the current application. No claim for improvement in exercise endurance or dyspnea is being sought.

2.4. Regulatory History

A number of interactions have occurred between the Division of Pulmonary, Allergy, and Rheumatology Products and GSK regarding the clinical, nonclinical, and chemistry, manufacturing, and controls aspects of UMEC/VI development. The Phase III clinical development program for UMEC/VI was designed to support global registration for the UMEC/VI combination for the maintenance treatment of COPD and to fully characterize the individual components. It was consistent with the requirements of 21 CFR 300.50 fixed-combination prescription drugs for humans. Feedback was also considered from regulatory discussions regarding BREO ELLIPTA (NDA 204275) for COPD and asthma. The following items highlight the most relevant milestones:

- **November 2009, Investigational New Drug (IND) application**: The UMEC/VI IND was submitted.
- **October 2010, End of Phase II meeting**: The design of the Phase III clinical trials was discussed, including the adequacy of the proposed clinical pharmacology and nonclinical data packages, and the clinical safety exposure planned at the time of NDA submission for UMEC monotherapy. At the meeting, the Division recommended exploring lower doses to further characterize the nominal dose and the dosing interval in the target patient population. This was addressed in a subsequent Phase IIb dose-ranging trial evaluating a lower range of doses of UMEC than previously evaluated. The dose and dose interval for

VI was determined by separate dose-ranging studies to support VI dose selection for UMEC/VI and BREO ELLIPTA.

- **January 2012, preNDA meeting**: The format and content of the NDA were discussed. The Division also discussed the need to describe the relevant patient population for the proposed combination product and indicated that the active-comparator studies and the endpoint of reduction in albuterol use would provide useful data. Known AESIs associated with muscarinic antagonists and beta-agonists for evaluation in the Phase III clinical development program were discussed and agreed (i.e., CV effects, other anticholinergic effects (e.g., urinary retention and ocular disorders) and beta-adrenergic effects (e.g., electrolyte imbalances and tremor). An evaluation of pneumonia was also requested. In addition to the adjudication of serious adverse events (SAEs) from the Phase III clinical development program proposed by GSK, the Division requested an analysis of MACE and respiratory-related events such as those conducted by other COPD programs.
- **December 2012, NDA submission**
- **May 2013, Mid-cycle review meeting**: The status of the NDA was shared. The Division noted that the rationale for proposing the UMEC/VI 125/25 mcg dose for approval was based in part on subgroup analyses which are considered to be exploratory in nature. On the basis of this discussion with the Division, GSK subsequently removed the higher dose from the labelling as part of this review cycle.

3. CLINICAL DEVELOPMENT PROGRAM

The Phase III development program was designed to investigate 2 doses of UMEC/VI, 62.5/25 and 125/25 mcg. The 2 doses of UMEC/VI were demonstrated to be similar with regard to efficacy and safety in the overall Phase III study population. As part of pre-planned subgroup analyses, the subpopulation of subjects demonstrating reversibility to albuterol (approximately 30% of enrolled patients) showed greater benefit with the higher dose based on lung function. As a result of this finding and further post-hoc analyses, both doses of UMEC/VI were initially proposed in the NDA. During the NDA review, revised labeling was submitted for the lower strength only as the subpopulation requires further delineation. The data for the higher dose are presented as they provide important information regarding the overall efficacy and safety of the UMEC/VI combination at double the UMEC dose.

3.1. Overview

The pharmacological, PK and toxicological effects of UMEC or VI when administered alone and in combination have been well characterized in a comprehensive range of nonclinical studies to support their long-term clinical use. See Appendix 10.1 for an overview of nonclinical pharmacology and toxicology. An overview of clinical pharmacology and PK studies is provided in Appendix 10.2. The PK profile for UMEC/VI is consistent with an inhaled medication with limited systemic exposure and rapid clearance. No dose adjustment for renal or hepatic impairment, age, gender, weight, ethnicity, or ICS use is warranted.

The UMEC/VI global clinical development program was constructed to provide evidence of efficacy, in terms of improvements in lung function and symptoms, in patients with COPD. As neither of the components is approved for treatment of COPD, studies designed to evaluate the

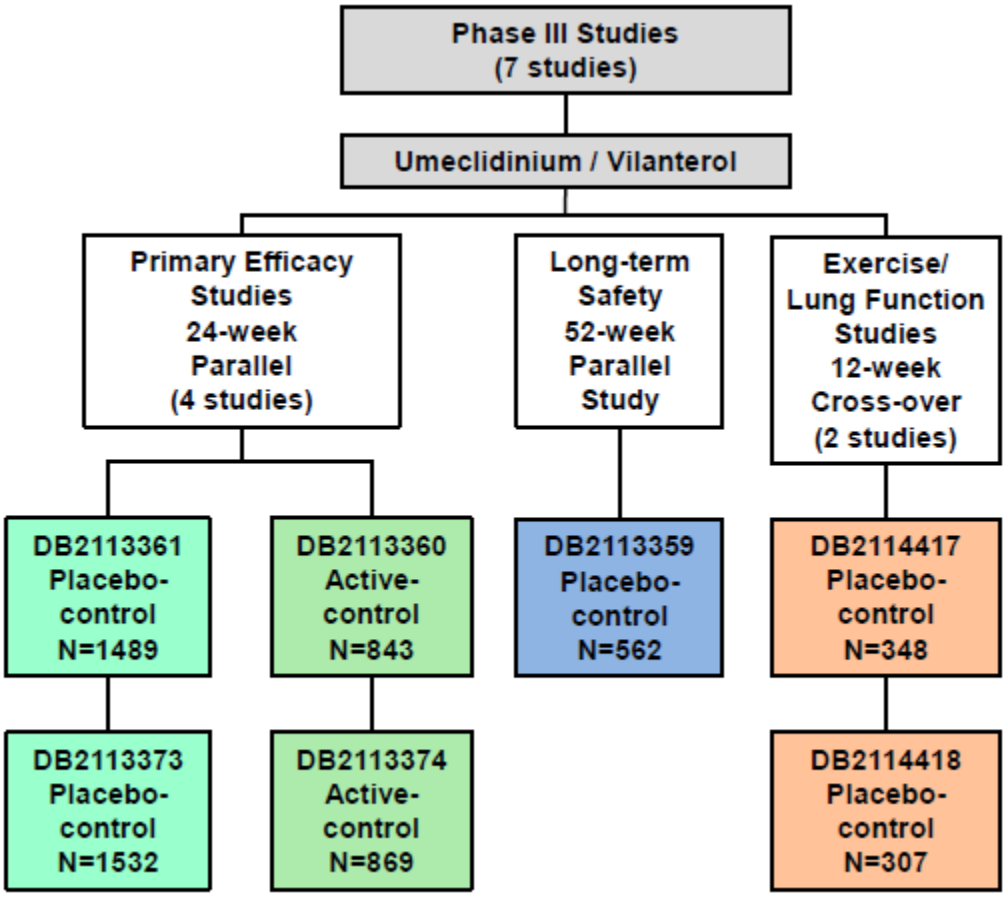
efficacy of the UMEC/VI combination and the efficacy of UMEC and VI individually, as well as the contribution of each component to the combination were included. Safety was assessed for UMEC/VI, UMEC, and VI compared with placebo as well as for UMEC/VI compared with UMEC and VI individually. In addition, the clinical development program included comparisons of UMEC/VI with tiotropium, an approved LAMA with a well established efficacy and safety profile.

The approach to develop UMEC/VI in parallel with the individual components was taken to best achieve the goal of providing a once-daily fixed-dose LAMA/LABA combination product in a single inhaler that optimizes treatment of airflow obstruction and offers improved compliance and convenience over the use of single long-acting bronchodilators from separate inhalers.

Six dose-ranging and dosing-interval studies were conducted for UMEC and VI separately to support the selection of the appropriate dose and dosing interval for the monotherapies and as components of UMEC/VI. The UMEC dose-ranging and dosing-interval studies are discussed in Section 3.2. The VI dose and dosing interval (25 mcg once-daily) selected as a component of UMEC/VI is the same as that selected for the LABA dose in the BREO ELLIPTA combination product which is approved in the US for the treatment of COPD (see Section 3.2).

The UMEC/VI clinical development program was principally comprised of 7 Phase III studies (Figure 10) conducted in 32 countries and involving approximately 6000 subjects. The four 24-week Primary Efficacy Studies and the 52-week Long-term Safety Study are the key studies discussed in this briefing document. The two 12-week Exercise/Lung Function Studies provide supportive lung function data and contribute to safety data.

Figure 10 Phase III Clinical Development Overview



Key features of the Phase III studies in Figure 10 are presented in the Overview of Clinical Efficacy (Section 1.4, Table 2). A placebo group was included in 2 of the Primary Efficacy Studies (studies 373 and 361) and the Long-term Safety Study (study 359) to allow for a comprehensive assessment of the safety of the active treatments compared to inactive treatment. Additionally, in the Primary Efficacy Studies, the placebo group allowed for full evaluation of the efficacy of the active treatments. The most likely potential risk to patients receiving placebo was worsening disease due to inadequate pharmacologic treatment. However, the studies included numerous safeguards to ensure that subjects receiving placebo were appropriately managed and were not at serious risk from participating in the study:

- Concurrent use of respiratory medications: Patients were allowed to continue their use of ICS if applicable. Additionally, subjects were provided with supplemental albuterol for use throughout the study for symptom management. Use of the short-acting anticholinergic ipratropium was also allowed in the Long-term Safety Study.
- A reduced exposure to placebo treatment compared with the active treatments (3:2 ratio of active to placebo [each active: 3; placebo: 2] in the Primary Efficacy Studies and a 2:1 ratio [each active: 2; placebo: 1] in the Long-term Safety Study)

- Exclusion of subjects with poorly controlled COPD. Subjects who were hospitalized for COPD within 12 weeks of screening and/or had an exacerbation of COPD during the Run-in period were not randomized. Additionally, in the Primary Efficacy Studies and Exercise/Lung Function Studies, any subjects who experienced a COPD exacerbation (defined as an acute worsening of symptoms of COPD requiring the use of any treatment other than study medication or rescue albuterol) during the treatment period were to be withdrawn to allow for proper management of the exacerbation. Patients with an exacerbation in the Long-term Safety Study may have remained in the study and short-course treatment of the exacerbation with standard therapy (e.g., oral corticosteroids and or antibiotics) was allowed.
- Exclusion of subjects with severe COPD requiring long-term oxygen therapy.
- Subjects' health status was monitored daily using an electronic diary card where subjects recorded any contact with a doctor or nurse about their COPD (Primary Efficacy Studies). In all studies, the study investigator's/site's contact name and number were provided and study participants were instructed to contact their investigator if COPD symptoms worsened.
- Subjects could be withdrawn from the study at any point for any reason (including poor control of their disease) or without giving a reason. In the Long-term Safety Study and Exercise/Lung Function Studies, a lower limit for airflow obstruction was specified (35% FEV_1 predicted) to exclude patients with very severe disease.

In addition to the studies shown in Figure 10, a 12-week UMEC monotherapy study and 6 additional studies which included a relevant UMEC or VI monotherapy arm contribute to safety evaluations (All COPD Grouping; 14 studies). A tabulation of key features for all 14 studies is provided in Appendix 10.4 (see also Section 5.1, Figure 35).

3.2. Selection of Dose and Dosing Interval for Umeclidinium and Vilanterol Monotherapy for Use in Phase III Trials

Selection of the doses of UMEC and VI for the UMEC/VI combination for evaluation in the Phase III trials was based on identification of doses with optimal benefit:risk profiles using data obtained from separate dose-ranging trials for UMEC and VI. This was considered a reasonable approach to dose selection for the combination as there were distinct mechanisms of action.

Six dose-ranging and dosing-interval studies of 7 to 28 days duration were conducted for UMEC and VI separately to support the selection of the appropriate dose and dosing interval for the monotherapies and as components of UMEC/VI (See Section 1.4, Table 1). Four were conducted in subjects with COPD, including 3 studies for UMEC (studies 073, 321, and 589) and 1 study for VI (study 045). Subjects (males and females) were 40 to 80 years old with a history of COPD, a ≥10 pack years smoking history, a post-albuterol FEV_1/FVC ratio of ≤0.70 and a post-albuterol FEV_1 of ≥35 and ≤70% of predicted normal. The primary endpoint in each of these studies was trough FEV_1.

Two additional studies were conducted in asthma subjects to support the VI dose and dosing interval selection, a dose-ranging study (study 575) and a dosing-interval study (study 310). These studies were conducted in male and female subjects with persistent asthma who had a pre-bronchodilator FEV_1 of ≥40% to ≤85% (study 310) or ≥40% to ≤90% (study 575) and were

using maintenance ICS therapy. These studies provide supportive information for dose selection of VI in COPD since an asthma population is highly responsive to beta-agonist bronchodilation.

3.2.1. Umeclidinium Dose and Dosing Interval Selection

3.2.1.1. Umeclidinium Dose Selection

UMEC doses ranging from 15.6 mcg to 1000 mcg once daily, representing a 64-fold range, were studied across the 3 dose-ranging studies in subjects with COPD. Doses of 125 mcg and below had AE profiles that were comparable with placebo while at doses of 250 mcg and above, AEs of headache, dry mouth, and cough were more common.

Results of the statistical analysis of trough FEV_1 (primary endpoint) from these studies are shown in Table 17. The bronchodilator response appeared consistent over the range of treatment durations tested in these studies (7 to 28 days), indicating that the steady-state pharmacodynamice (PD) effect of UMEC is observed at most after 7 days of treatment (corresponding to trough FEV_1 at Day 8).

Considering the data across studies, a dose ordering for trough FEV_1 was observed (Table 3). The dose of 125 mcg provided a near maximal response in these studies. The 62.5 mcg appeared to be on the ascent of the dose response with lower doses providing less improvement. To further evaluate the efficacy and safety of UMEC in larger, longer term studies, 2 doses of UMEC were selected for Phase III. The dose of 125 mcg was selected as it provided near maximal efficacy, and a lower dose of 62.5 mcg was also selected. Further data from the dose-ranging studies are provided below.

Table 17 LS Mean Difference from Placebo for Change from Baseline for Trough FEV_1 (Studies 073, 321, and 589)

Study/Day	LS Mean Difference from Placebo for Change from Baseline in Trough FEV_1 (mL) (95% CI) [n]							
	Once-daily UMEC dose (mcg)							
	15.6	31.25	62.5	125	250	500	1000	TIO [a]
073 at Day 15			128 (60, 196) [34]	147 (77, 216) [33]	95 (27, 162) [35]	140 (74, 205) [37]	186 (113, 259) [29]	105 (37, 173) [34]
321 at Day 8	113 (58,168) [58]	101 (45,158) [56]	124 (68,179) [59]	183 (127,239) [59]				101 (45,157) [56]
589 at Day 29				159 (088,229) [64]	168 (99,238) [68]	150 (80,220) [64]		

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; TIO=tiotropium; UMEC=umeclidinium bromide

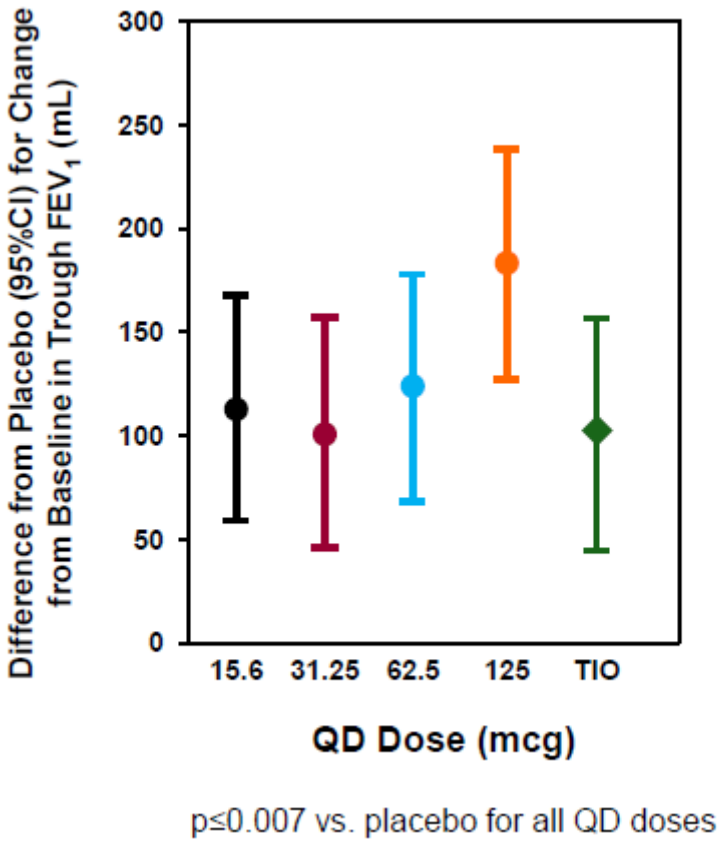
Note: Studies 073 and 321 were cross-over studies.

a. Tiotropium was administered open-label.

As minimal additional benefit in terms of trough FEV_1 response was demonstrated at once-daily UMEC doses above 125 mcg, the focus in this briefing document will be on study 321 which evaluated a lower range of once-daily doses (15.6 to 125 mcg).

A dose ordering for bronchodilator effect was demonstrated in study 321. The magnitude of the difference from placebo for the 125 mcg dose was substantially greater than that observed for lower UMEC doses or tiotropium (Table 17 and Figure 11).

Figure 11 Placebo-Adjusted LS Mean Change from Baseline for Trough FEV_1 (mL) on Day 8: Once-daily UMEC Doses and Tiotropium (Study 321)

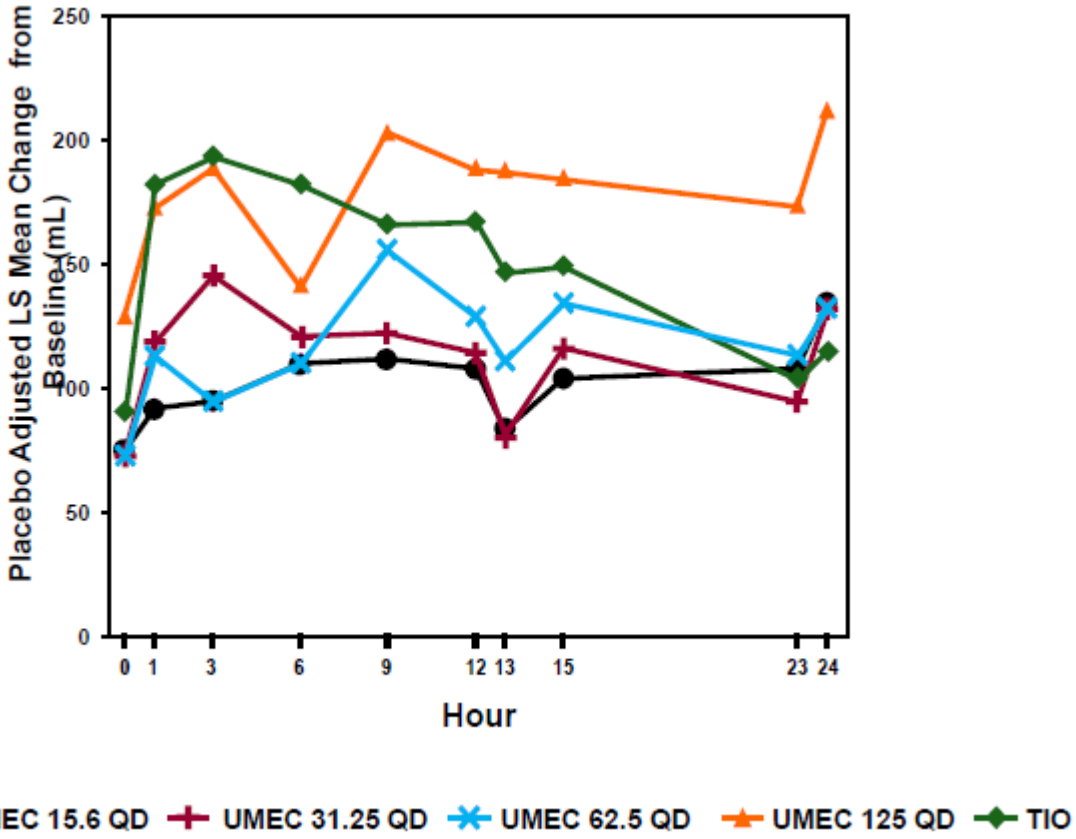


Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; QD=once-daily; TIO=tiotropium; UMEC=umeclidinium bromide
Note: Tiotropium was administered open-label.

Trough FEV_1 does not convey the full picture of bronchodilation offered to patients, and thus the 24-hour serial FEV_1 profiles were also evaluated. These profiles showed UMEC doses of 62.5 and 125 mcg were the most similar in efficacy to tiotropium, with the bronchodilator effect of the 62.5 mcg dose generally less and the effect of the 125 mcg dose generally greater than that of tiotropium over time (Figure 12). Over the latter half of the dosing interval, a more favorable

profile was observed with the 62.5 and 125 mcg doses compared with the lower doses of 15.6 and 31.25 mcg.

Figure 12 Placebo-Adjusted LS Mean Change from Baseline in FEV_1 Over Time on Day 7: Once-Daily UMEC Doses and Tiotropium (Study 321)



Abbreviations: FEV_1=forced expiratory volume in 1 second; LS=least squares; QD=once-daily; TIO=tiotropium; UMEC=umeclidinium bromide
Note: Totropium was administered open-label.

The 0 to 24 hour weighted mean FEV_1 data also demonstrated dose ordering (Table 18). The magnitude of the differences from placebo for the 62.5mcg and 125 mcg doses were more similar to the tiotropium active control than the 15.6 and 31.25 mcg doses.

Table 18 LS Mean Difference from Placebo for Change from Baseline for 0 to 24 Hour Weighted Mean FEV_1 (mL) on Day 7 (Study 321)

	Once-daily UMEC dose (mcg)				Tiotropium [a]
Day 7	15.6 mcg N=60	31.25 mcg N=57	62.5 mcg N=59	125 mcg N=60	18 mcg N=56
Difference from placebo (95% CI)	116 (72,160)	118 (73,163)	132 (87,178)	173 (129,217)	157 (113,202)

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in one second; LS=least square; UMEC=umeclidinium bromide
a. Tiotropium was administered open-label.

The analysis of rescue use also provides supportive information. Dose ordering was observed across the once-daily doses with the 125 mcg dose demonstrating the largest reduction in use compared with placebo (Table 19), and an effect comparable to that noted with tiotropium

Table 19 LS Mean Difference from Placebo for Mean Number of Puffs/Day of Rescue Albuterol (Study 321)

	Once-daily UMEC dose (mcg)				Tiotropium [a]
	15.6 mcg N=60	31.25 mcg N=57	62.5 mcg N=59	125 mcg N=60	18 mcg N=56
Difference from placebo (95% CI)	-0.254 (-0.682,0.173)	-0.283 (-0.717,0.150)	-0.464 (-0.894,-0.034)	-0.804 (-1.231,-0.376)	-0.980 (-1.417,-0.543)

Abbreviations: CI=confidence interval; LS=least square; UMEC=umeclidinium bromide
a. Tiotropium was administered open-label.

3.2.1.2. Umeclidinium Dosing Interval Selection

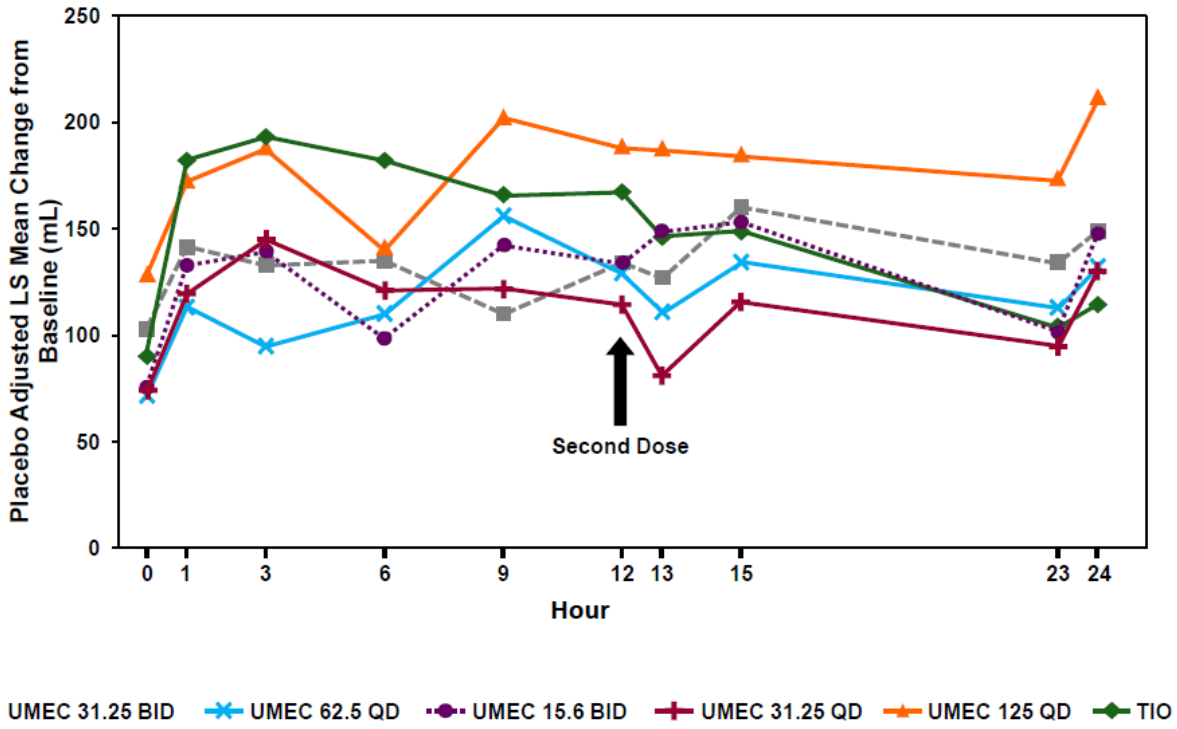
Two of the dose-ranging studies (studies 321 and 073) evaluated once- and twice-daily dosing and provide substantial evidence of the duration of action supporting once-daily administration of UMEC. In both studies, the once-daily doses were administered in the morning and twice-daily doses were administered in the morning and evening, approximately 12 hours apart.

Overall, the findings from studies 321 and 073 support selection of a once-daily dosing interval by demonstrating that the FEV_1 profiles with once-daily dosing showed consistent improvements in FEV_1 relative to placebo over 24 hours and that twice-daily dosing of UMEC at the same nominal dose did not provide meaningful benefit over once-daily dosing.

Study 321

The 24-hour serial FEV_1 profiles for study 321 allow for comparisons of the total daily UMEC dose administered once daily or administered as 2 divided doses and for comparison with tiotropium. The serial FEV_1 profile with once-daily dosing showed consistent improvements in FEV_1 relative to placebo over 24 hours (Figure 13). Twice-daily dosing of UMEC at the same nominal dose did not provide substantially greater benefit over once-daily dosing in the latter 12 hours of the dosing interval. Notably, administration of a second dose of UMEC at 12 hours following the morning dose did not result in an appreciable change in FEV_1 in the subsequent 12 hours. Furthermore, the improvements compared with placebo in FEV_1 observed at time points over the first 12 hours were maintained at time points over the second 12 hours with UMEC once daily.

Figure 13 **Placebo-Adjusted LS Mean Change from Baseline for Trough FEV_1 Over Time on Day 7: UMEC Once-Daily and Twice-Daily Doses and Tiotropium (Study 321)**



Abbreviations: BID=twice-daily, CI=confidence interval; FEV1=forced expiratory volume in 1 second; LS=least squares; QD=once daily; TIO=tiotropium; UMEC=umeclidinium bromide
Note: Totropium was administered open-label.

The mean ratios of evening (12 to 24 hours) to morning (0 to 12 hours) weighted mean FEV_1 values were approximate to 1.0 for all once-daily UMEC doses, indicating that the 24-hour duration of effect is an intrinsic property of the compound (Table 20). Similar ratios across both the once- and twice-daily dosing regimens provide further support for a once-daily dosing interval.

Table 20 Statistical Analysis of Change from Baseline in Weighted Mean FEV_1 (L): Difference in Treatment Effect Between 12 to 24 hours and 0 to 12 hours at Day 7 (Study 321)

	Once-daily UMEC (mcg)				Twice-daily UMEC (mcg)		Once-daily tiotropium [a] 18 mcg
	15.6 N=60	31.25 N=57	62.5 N=59	125 N=60	15.6 N=56	31.25 N=58	N=56
Column vs. Placebo Absolute Difference [b]	0.018	-0.007	0.021	0.010	0.019	0.028	-0.036
95% CI	(-0.040, 0.076)	(-0.067, 0.053)	(-0.038, 0.080)	(-0.048, 0.069)	(-0.041, 0.078)	(-0.030, 0.087)	(-0.095, 0.023)
Ratio [c]	1.176	0.943	1.162	1.059	1.147	1.215	0.793

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; TIO=tiotropium; UMEC=umeclidinium bromide

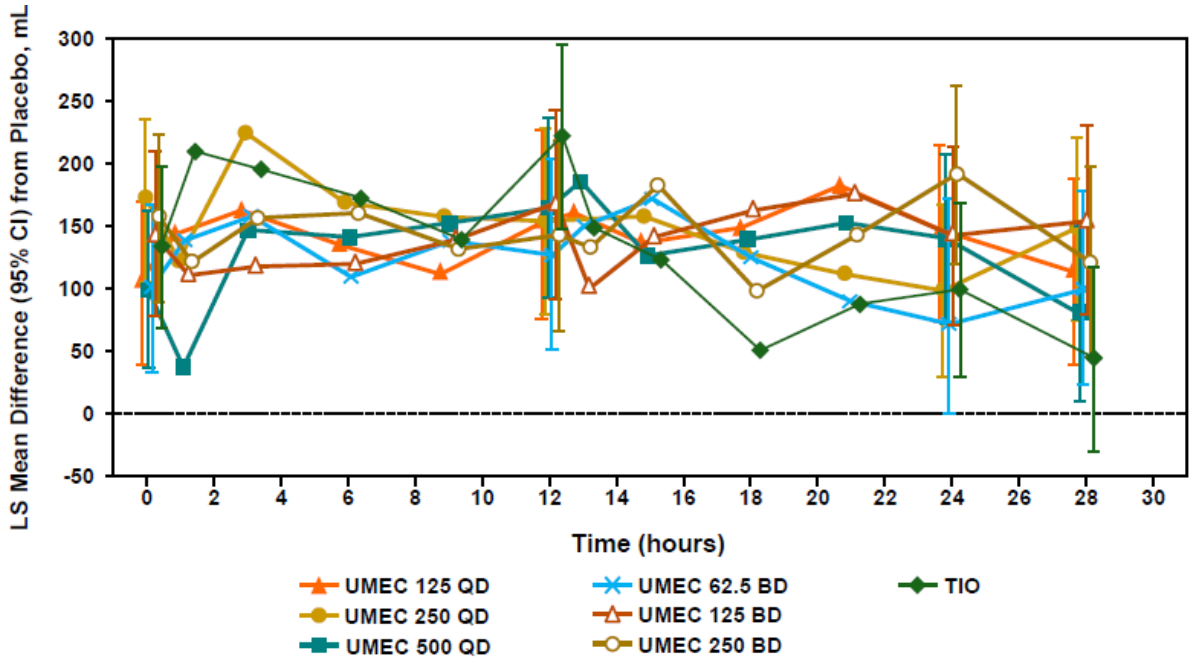
a. Tiotropium was administered open-label.
b. The column vs. placebo difference is calculated as the difference in change from baseline in weighted mean FEV_1 between active and placebo at 12-24 hours minus the difference in change from baseline in weighted mean FEV_1 between active and placebo at 0-12 hours.
c. The ratio is the difference in change from baseline in weighted mean FEV_1 between active and placebo at 12-24 hours divided by the difference in change from baseline in weighted mean FEV_1 between active and placebo at 0-12 hours.

Study 073

In study 073, once-daily doses of 62.5, 125, 250, 500, and 1000 mcg and twice-daily doses of 62.5, 125, and 250 mcg were evaluated over 14 days.

Similar to study 321, evaluation of the serial FEV_1 response curves did not indicate twice-daily dosing of UMEC provided additional benefit in bronchodilator response over once-daily dosing for nominal dose comparisons (Figure 14).

Figure 14 Placebo-Adjusted LS Mean Change from Baseline for Trough FEV_1 Over Time on Day 14: UMEC Once-Daily and Twice-Daily Doses and Tiotropium (Study 073)



Abbreviations: BD=twice-daily; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; QD=once daily; TIO=tiotropium; UMEC=umeclidinium bromide
Note: Tiotropium was administered open-label.

Additionally, the mean ratios of evening (12 to 24 hours) to morning (0 to 12 hours) weighted mean FEV_1 values shown in Table 21 were supportive of a once-daily dosing interval with the exception of the 250 mcg once-daily dose which had a lower than expected response at 20 and 24 hours in this study.

Table 21 Statistical Analysis of Change from Baseline in Weighted Mean FEV_1 (L): Difference in Treatment Effect Between 12 to 24 hours and 0 to 12 hours at Day 14 (Study 073)

	UMEC Once-daily (mcg)					UMEC Twice-daily (mcg)			Once-daily tiotropium [a] 18 mcg N=35
	62.5 N=35	125 N=34	250 N=36	500 N=38	1000 N=32	62.5 N=34	125 N=37	250 N=33	
Column vs. Placebo absolute difference [b]	-0.030	0.023	-0.036	0.006	0.039	-0.006	0.017	-0.002	-0.076
95% CI	(-0.095, 0.035)	(-0.042, 0.089)	(-0.101, .028)	(-0.056, 0.069)	(-0.030, 0.108)	(-0.074, 0.062)	(-0.049, 0.083)	(-0.069, 0.064)	(-0.141, -0.011)
Ratio [c]	0.807	1.198	0.751	1.050	1.317	0.953	1.125	0.983	0.542

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; TIO=tiotropium; UMEC=umeclidinium bromide

Note: Absolute differences >0 indicate a larger treatment effect between 12 to 24 hours.

a. Tiotropium was administered open-label.
b. The column vs. placebo difference is calculated as the difference in change from baseline in weighted mean FEV_1 between active and placebo at 12-24 hours minus the difference in change from baseline in weighted mean FEV_1 between active and placebo at 0-12 hours.
c. The ratio is the difference in change from baseline in weighted mean FEV_1 between active and placebo at 12-24 hours divided by the difference in change from baseline in weighted mean FEV_1 between active and placebo at 0-12 hours.

3.2.2. Vilanterol Dose and Dosing Interval Selection

The VI dose and dosing interval (25 mcg once-daily) selected as a component of UMEC/VI is the same as that selected for the LABA dose in the BREO ELLIPTA combination product which is approved in the US for the treatment of COPD. The dose and dosing interval selections for VI were based on 3 Phase IIb studies, 1 in subjects with COPD (study 045) and 2 in subjects with asthma (studies 575 and 310). Only results for the COPD study (study 045) are presented in this briefing document. However, the results from the asthma dose-ranging studies were consistent with those of the COPD study, supporting a selection of the VI 25 mcg dose and the once-daily dosing interval for both UMEC/VI and BREO ELLIPTA.

Study 045 demonstrated a dose-related increase in trough FEV_1 over the range of once-daily doses tested over 28 days (3, 6.25, 12.5, 25 and 50 mcg) (Table 22).

Table 22 LS Mean Difference from Placebo for Change from Baseline for Trough FEV_1 (mL) on Day 29 (Study 045)

	Once-Daily VI (mcg)				
	3 N=99	6.25 N=101	12.5 N=101	25 N=101	50 N=99
Difference vs. Placebo 95% CI	92 39, 144	98 46, 150	110 057, 162	137 085, 190	165 112, 217

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; VI=vilanterol

VI 25 and 50 mcg once daily were associated with greater improvements in secondary and other efficacy parameters including 0 to 24 hour weighted mean FEV_1, individual serial FEV_1 time points, and the percentage of symptom-free periods. All VI doses were well tolerated throughout the study period. Based on the efficacy findings and the overall benefit:risk profile, the 25 mcg dose was chosen as the dose with the optimal benefit-risk profile.

3.3. Primary Efficacy Studies

The selected UMEC (62.5 and 125 mcg) and VI (25 mcg), and UMEC/VI (62.5/25 and 125/25 mcg) doses were evaluated in the 4 Primary Efficacy Studies as shown in Table 23.

Table 23 Treatment Groups: Primary Efficacy Studies

Placebo-controlled Studies	
Study 373	Study 361
UMEC/VI 62.5/25 mcg	UMEC/VI 125/25 mcg
UMEC 62.5 mcg	UMEC 125 mcg
VI 25 mcg	VI 25 mcg
Placebo	Placebo
Active-comparator Studies	
Study 360	Study 374
UMEC/VI 125/25 mcg	UMEC/VI 125/25 mcg
UMEC/VI 62.5/25 mcg	UMEC/VI 62.5/25 mcg
VI 25 mcg	UMEC 125 mcg
Tiotropium	Tiotropium

Abbreviations: UMEC=umeclidinium bromide; VI=vilanterol

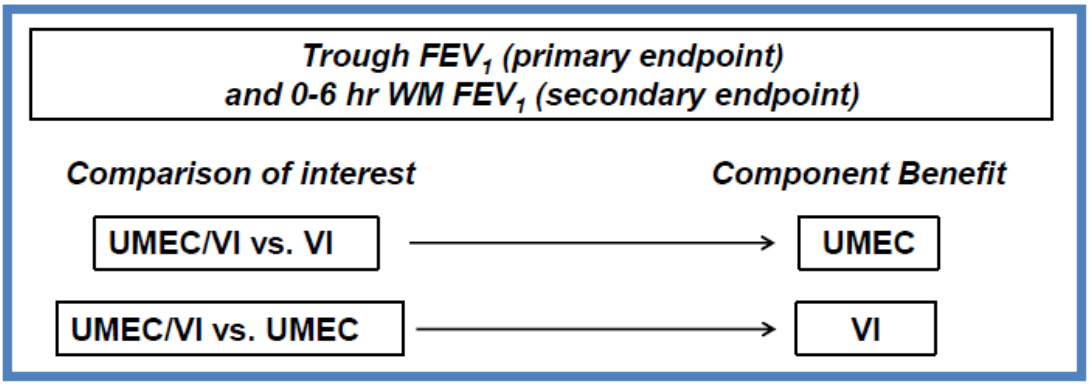
Evaluation of the Contribution of the UMEC and VI to the Efficacy of the UMEC/VI Combination for Improvement in Airflow Obstruction

As UMEC/VI is a combination product, the benefit of each component to the efficacy of the combination to improve airflow obstruction must be demonstrated. Comparisons used to evaluate the benefit of UMEC and VI to UMEC/VI are shown in Figure 15.

The Primary Efficacy Studies allowed for the evaluation of the contribution of the components to both doses of the combination. Analyses were based on the primary efficacy endpoint of trough FEV_1 and the secondary endpoint of 0 to 6 hour weighted mean FEV_1. The contribution of UMEC 62.5 mcg (comparison of UMEC/VI 62.5/25 mcg vs. VI 25 mcg) was evaluated in study 373 and study 360. The contribution of VI (comparison of UMEC/VI 62.5/25 mcg vs. UMEC 62.5 mcg) was evaluated in study 373.

Trough FEV_1 results for the 2 Exercise/Lung Function Studies provide additional supportive data to evaluate the benefit of each component to the combination (see Section 4.4.4).

Figure 15 Comparisons Evaluating the Benefit of Each Component to the Combination



Abbreviations: FEV_1=forced expiratory volume in 1 second; UMEC=umeclidinium bromide; VI=vilanterol; WM=weighted mean

Efficacy of UMEC and VI for Improvement in Airflow Obstruction

Comparisons of UMEC and VI with placebo in studies 373 and 361 provide the principal data to evaluate the safety and efficacy of the component monotherapies.

3.3.1. Study Design

All 4 Primary Efficacy Studies were randomized, multicenter, parallel-group studies with a 24-week treatment period. In the placebo-controlled trials, UMEC/VI, UMEC, VI and matching placebo were administered in a double-blind fashion once daily in the morning via the ELLIPTA DPI.

A double dummy design was used for the active-comparator studies because these studies included delivery with the ELLIPTA DPI and the HandiHaler DPI. Blister packaged capsules of tiotropium or its corresponding placebo were administered once daily in the morning via the HandiHaler DPI and UMEC/VI, UMEC, VI or placebo were administered once daily in the morning via the ELLIPTA DPI. Each patient took one dose from the Handihaler DPI and one dose from the ELLIPTA DPI each morning. Blinding of tiotropium was imperfect, however, because the tiotropium capsules had trade markings but the placebo capsules, while closely matched in color, did not have trade markings. Whether patients would notice, and rightly or wrongly attach any significance to the capsule markings, is unclear. As these studies were of parallel group design, the capsule type was consistent for each patient for the duration of the study. Both the tiotropium and placebo blister packages were covered with opaque over-labels with the intent of shielding information appearing on the blister packaging of tiotropium. The HandiHaler DPIs were covered with labels in order to mask identifying marks on the inhaler. Dosing in the clinic was administered without the presence of staff involved with safety and efficacy assessments to guard against the possibility that they would observe and draw correct inferences from the presence or absence of markings on capsules removed from the blisters.

The randomization ratio differed for the placebo-controlled (3:3:3:2 [each active 3; placebo 2) vs. active-comparator (1:1:1:1) studies. For all 4 studies, subjects who met the eligibility criteria at Screening (Visit 1) entered a 7- to 10-day Run-in Period, and those who continued to meet eligibility criteria entered a 24-week Treatment Period. Clinic visits were at Screening, Randomization (Day 1), Day 2, after 4, 8, 12, 16, and 24 weeks, and 1 day after the Week 24 visit (Visits 1 to 9, respectively). Additionally, a Safety Follow-up assessment was conducted either by telephone call or clinic visit approximately 7 days after the end of the study treatment (Visit 9 or Early Withdrawal, if applicable). The total duration of subject participation, including the Follow-up assessment was approximately 26 to 27 weeks.

Subjects were allowed concurrent use of ICS at a stable dose and as-needed use of short-acting bronchodilators to provide adequate background pharmacotherapy for COPD.

3.3.2. Enrollment Criteria

The enrollment criteria for the Primary Efficacy Studies were the same across all 4 studies. Male and female subjects ≥40 years of age with a clinical history of COPD were eligible for participation. Subjects were required to have an extensive cigarette smoking history (≥10 pack-years) and the presence of moderate to very severe airflow obstruction (a post-albuterol FEV_1 of ≤70% of predicted normal values and a post-albuterol FEV_1/FVC ratio of <0.70).

Subjects were required to have symptoms upon entry based on a mMRC dyspnea score of ≥2. An mMRC score of 2 is defined as walking slower than people of the same age on the level or having to stop for breath when walking at own pace on a level surface.

Subjects had stable disease and were excluded if they had been hospitalized due to a COPD exacerbation or pneumonia within 12 weeks prior to Screening and/or had poorly controlled COPD (defined as acute worsening of COPD that was treated with oral corticosteroids or antibiotics within 6 weeks prior to Screening) and/or had experienced a LRTI that required the use of antibiotics within 6 weeks prior to Screening. Subjects with a current diagnosis of asthma, α1-antitrypsin deficiency, any clinically significant uncontrolled disease as determined by the investigator, or any clinically significant laboratory finding were excluded. Subjects were also excluded who had a medical condition such as narrow angle-glaucoma, prostatic hypertrophy, or bladder neck obstruction that, in the opinion of the investigator, contraindicated study participation or the use of an inhaled anticholinergic.

There were no specific exclusionary criteria regarding CV risk other than exclusion for clinically significant uncontrolled CV disease based on the medical judgment of the study investigator and/or abnormal, clinically significant ECG findings.

Concurrent use of systemic corticosteroids, long-acting bronchodilators, including theophyllines, was not allowed and previous use of UMEC and/or VI was not allowed. Concurrent use of ICS at a stable dose was allowed through the duration of the study.

3.3.3. Withdrawal Criteria

Across the 4 Primary Efficacy Studies, subjects were required to be withdrawn from the study if they experienced a clinically important laboratory, 12-lead ECG, or Holter finding. Additionally, subjects were to be withdrawn from the study if they experienced a COPD exacerbation (defined as an acute worsening of symptoms of COPD requiring the use of any treatment beyond study drug or rescue medication).

3.3.4. Efficacy Measures

3.3.4.1. Lung Function

Primary and secondary lung function measures of trough FEV_1 and weighted mean FEV_1 over 0 to 6 hours post-dose, respectively, were used to support the indication for the maintenance treatment of airflow obstruction.

Primary Endpoint

The primary endpoint for all 4 studies was trough FEV_1 obtained at Day 169 (Week 24). This was chosen to provide a robust, well established, and objective means of demonstrating bronchodilator efficacy of UMEC/VI and its components and for demonstrating the contribution of each component to the efficacy of UMEC/VI. Trough FEV_1 is defined as the mean of the FEV_1 values obtained at 23 and 24 hours after dosing on Day 168 (Week 24), allowing for evaluation of bronchodilator efficacy at the end of the once-daily dosing interval.

Secondary Endpoint

The secondary endpoint of 0 to 6 hour weighted mean FEV_1 at Day 168, calculated based on serial FEV_1 assessments obtained 15 and 30 minutes, and 1, 3, and 6 hours post-dose, evaluated bronchodilator efficacy over the initial part of the dosing interval in all 4 studies. The 0 to 6 hour weighted mean was derived by calculating the area under the FEV_1 time curve over the nominal time points of 0 hour, 15 and 30 min, 1, 3 and 6 hour, using the trapezoidal rule, and then dividing by the actual time between dosing and the 6 hour assessment. For post-dose observations the actual time of assessment relative to the time of dosing was used for the calculation.

Additional Measures of Lung Function

Serial FEV_1 at each time point over 6 hours was evaluated in all 4 studies. Serial spirometry over 24 hours was obtained in a subset of subjects (twenty-four hour [TFH] subset) from selected study sites in the placebo-controlled studies (n=197 in study 373 and n=199 in study 361). These assessments were used for evaluation of lung function over the dosing period.

Serial and trough FVC, peak FEV_1, and proportion of subjects achieving an increase in FEV_1 of ≥12 % and ≥200 mL above baseline at any time during 0 to 6 hour postdose on Day 1 were also evaluated in all 4 studies. Results for these additional lung function endpoints, which will not be discussed in this briefing document, were consistent with those for the primary and secondary efficacy endpoints.

3.3.4.2. Patient-reported Measures and Health-related Quality of Life

Consistent with other approved LAMA and LABA medications, supportive findings for the patient-reported measures of rescue albuterol use and the SGRQ measure of health-related quality of life are proposed for inclusion in the Clinical Trials section of the prescribing information for ANORO ELLIPTA. Claims are not being sought for any of the additional patient-reported measures discussed below.

Rescue Albuterol Use

Rescue albuterol use is a commonly used measure of symptom control. The number of puffs of rescue medication used each day was recorded by subjects in an electronic diary.

St. George's Respiratory Questionnaire

The SGRQ [Jones, 1992] is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on the subject's health-related quality of life. It has been used extensively in clinical trials to characterize the impact of various COPD medicines on health-related quality of life.

The SGRQ contained 76 items grouped into 3 domains (symptoms, activity, and impacts). The SGRQ total score is calculated as the sum of the weighted scores from all 76 items, divided by the maximum possible score for the SGRQ, multiplied by 100. A lower SGRQ score indicates better health status. The MCID for SGRQ is a -4 unit difference for comparisons with placebo [Jones, 2005].

Transition Dyspnea Index

The TDI was developed to measure changes from a baseline state of dyspnea over time and has been used widely in COPD trials to assess the effect of treatments on dyspnea [Mahler, 2005]. The TDI score encompasses ratings for 3 different categories that provoke breathlessness: functional impairment; magnitude of task, and magnitude of effort. Scores for each of the categories range from minus three (major deterioration) to plus three (major improvement) and includes a zero score to indicate "no change". For the TDI the 3 category scores are added to obtain a total TDI focal score ranging from minus nine to plus nine. The MCID for the TDI is a 1 unit difference for comparisons with placebo [Witek, 2003].

SOBDA Questionnaire

The SOBDA instrument is a newly designed 13-item patient-reported outcome measure developed by GSK to be administered as a daily electronic diary. It is designed to assess the impact of pharmacologic therapy on shortness of breath with daily activities in patients with COPD [Howard, 2012].

3.3.4.3. COPD Exacerbations

The clinical development program was not specifically designed to evaluate the effect of treatments on COPD exacerbations and subjects in the Primary Efficacy Studies were withdrawn

if an exacerbation occurred. A COPD exacerbation was defined as an acute worsening of symptoms of COPD requiring the use of any treatment beyond study drug or rescue albuterol.

3.3.5. Safety Measures

Safety assessments included the reporting of AEs, routine clinical laboratory assessments, evaluation of vital signs, and 12-lead ECG measurements. Holter monitoring was obtained in the same subset of subjects in the placebo-controlled studies who were included in 24-hour serial FEV_1 evaluations (TFH subset).

3.3.6. Statistical Methods

3.3.6.1. Description of Analysis Populations

The intent-to-treat (ITT) Population is the population of primary interest for the Primary Efficacy Studies and all presentations in this briefing document except for 24-hour serial FEV_1 and Holter ECG data. The definition of the ITT population, all subjects randomized to treatment who received at least 1 dose of randomized study drug in the treatment period, is consistent across all Primary Efficacy Studies, except study 360 where efficacy data, but not safety data, were excluded from the ITT population for 20 subjects from 1 site due to significant deviations from Good Clinical Practice which were identified by GSK. Analyses based on exclusion of this site did not substantively alter the results compared with those including this site.

The TFH subset is the population of interest for the 24-hour serial FEV_1 and Holter ECG data.

Outcomes are reported according to the randomized treatment allocation.

3.3.6.2. Treatment Comparisons

For the 2 placebo-controlled Primary Efficacy Studies, the treatment comparisons were:

- UMEC/VI vs. placebo,
- UMEC vs. placebo,
- VI vs. placebo,
- UMEC/VI vs. VI, and
- UMEC/VI vs. UMEC.

For the active-comparator Primary Efficacy Studies, the treatment comparisons were:

- UMEC/VI 125/25 mcg vs. tiotropium,
- UMEC/VI 125/25 mcg vs. VI 25 mcg or UMEC,
- UMEC/VI 62.5/25 mcg vs. tiotropium, and
- UMEC/VI 62.5/25 mcg vs. VI 25 mcg or UMEC.

3.3.6.3. Multiple Comparisons and Multiplicity

Within each of the 4 primary studies, to account for multiplicity across treatment comparisons and primary and secondary endpoints, a step-down closed testing procedure was applied, whereby inference for a test in the pre-defined hierarchy was dependent upon statistical significance having been achieved for the previous tests in the hierarchy. If at any point in the hierarchy a comparison did not demonstrate statistical significance, all further statistical analyses were fully described but were not inferential. If statistical significance was achieved for all comparisons in the hierarchy, inference is drawn from all other treatment comparisons in the study with no adjustment for multiplicity.

The order of tests included in the hierarchy for each Primary Efficacy Study is provided in Appendix 10.3.

For the placebo-controlled studies, the hierarchy consisted of the treatment comparisons identified in Section 3.3.6.2, performed in that order on the primary endpoint (trough FEV_1) and then on the secondary endpoint (0 to 6 hour weighted mean FEV_1).

For the active-comparator studies, the hierarchy consisted of the comparisons for the UMEC/VI 125/25 mcg dose (identified in Section 3.3.6.2) for the primary endpoint (trough FEV_1) and the secondary endpoint (0 to 6 hour weighted mean FEV_1), followed by the comparisons for the UMEC/VI 62.5/25 mcg dose on these endpoints.

Statistical significance was achieved at all points in the hierarchy for all but one of the Primary Efficacy Studies. For this study (study 374), some results cannot be considered inferential according to the strict terms of the hierarchy. The results from individual studies were reported in their entirety (i.e., treatment difference, least squares [LS] means, 95% CIs and p-values), with notations when inference could not be made based on failure of a prior test in the hierarchy.

3.3.6.4. Primary and Secondary Efficacy Analyses

The primary endpoint of trough FEV_1 on Day 169 was analyzed using a mixed model repeated measures (MMRM) analysis, including covariates of baseline FEV_1, smoking status, Day, center group, treatment, Day by baseline interaction and Day by treatment interaction, where Day is nominal. The model used all available trough FEV_1 values recorded on Days 2, 28, 56, 84, 112, 168 and 169. Missing data were not directly imputed in this analysis; however, all non-missing data for a subject were used within the analysis to estimate the treatment effect for trough FEV_1 on Day 169.

The secondary endpoint of 0-6 hour weighted mean FEV_1 was analyzed similarly.

3.3.6.5. Missing Data

In the 4 Primary Efficacy Studies, subjects were required to be withdrawn from the study if they experienced a clinically important laboratory, 12-lead ECG, or Holter finding. Additionally, subjects were to be withdrawn from the study if they experienced a COPD exacerbation (defined as an acute worsening of symptoms of COPD requiring the use of any treatment beyond study drug or rescue albuterol). Subjects could also be withdrawn in the case of an AE or lack of

efficacy or if the subject withdrew consent. Some subjects were lost to follow-up. None of the subjects were assessed for efficacy endpoints following withdrawal from the study.

To explore the robustness of the conclusions from the primary MMRM analysis to the impact of missing data following withdrawal from the study, several sensitivity analyses were conducted using multiple imputation (MI) methods. These are fully described in Appendix 10.3.2.

3.4. Long-Term Safety Study

3.4.1. Study Design

Study 359 was a randomized, double-blind, parallel-group, placebo-controlled, 52-week safety study of UMEC/VI 125/25 mcg and UMEC 125 mcg.

Subjects who met the eligibility criteria at Screening entered a 7- to 10-day Run-in Period. Subjects who continued to meet eligibility criteria were randomized in a 2:2:1 ratio to receive UMEC/VI 125/25 mcg, UMEC 125 mcg, or placebo for a 52-week Treatment Period. There were a total of 7 study visits. Clinic visits were at Screening (Visit 1), Randomization (Visit 2), and at 1, 3, 6, 9, and 12 months (Visits 3 through 7). A follow-up phone contact was conducted approximately 1 week after Visit 7 or the Early Withdrawal Visit, if applicable. The total duration of subject participation was approximately 54 weeks.

Concurrent use of systemic corticosteroids, long-acting bronchodilators, including theophyllines, was not allowed and previous use of UMEC and/or VI was not allowed. Subjects were allowed concurrent use of ICS at a stable dose and as-needed use of short-acting bronchodilators to provide adequate background pharmacotherapy for COPD.

3.4.2. Enrollment Criteria

Enrollment criteria were similar to those described in Section 3.3.2 for the Primary Efficacy Studies except for the limits applied for post-bronchodilator FEV_1 (≥35 and ≤80% of predicted normal values) and no criterion for an mMRC dyspnea score. The lower limit of trough FEV_1 was applied to ensure that patients with very severe disease did not receive placebo treatment in this 52-week study.

3.4.3. Withdrawal Criteria

As described for the Primary Efficacy Studies, subjects were required to be withdrawn from the study if they experienced a clinically important laboratory, 12-lead ECG, or Holter finding. Unlike the Primary Efficacy Studies, subjects were not required to withdraw because of a COPD exacerbation.

3.4.4. Assessments

Safety assessments included the reporting of AEs, routine clinical laboratory assessments, evaluation of vital signs, 12-lead ECG measurements, and 24-hour Holter monitoring in all subjects.

Trough FEV_1, supplemental bronchodilator use (albuterol and/or ipratropium bromide), the percentage of rescue-free days, COPD exacerbations, and trough FVC were assessed. Trough FEV_1 data are presented in this briefing document.

3.4.5. Statistical Methods

3.4.5.1. Description of Analysis Population

The ITT Population, as defined for the Primary Efficacy Studies (Section 3.3.6.1), is the population of primary interest for this study.

3.4.5.2. Statistical Analyses

No efficacy endpoints were specified. The study sample size was based on providing an acceptable number of patients treated with UMEC/VI and UMEC for long-term evaluations of safety. As such, the protocol specified that formal statistical hypothesis testing would not be performed.

Analyses of the pre-specified safety endpoint of trough FEV_1 are provided as evidence of persistence of efficacy of UMEC/VI and UMEC over 12 months.

3.5. Exercise/Lung Function Studies

Two 12-week Exercise/Lung Function Studies provide supportive lung function data although, as previously stated, no claim for improvement in exercise endurance is being sought.

3.5.1. Study Design

The Exercise/Lung Function Studies (studies 417 and 418) were randomized, double-blind, placebo-controlled, 2-period (12 weeks per period), incomplete block cross-over studies designed to evaluate the effect of UMEC/VI (62.5/25 and 125/25 mcg) on EET and lung function.

Subjects who met the eligibility criteria at Screening (Visit 1) entered a 12- to 21-day Run-in Period. Subjects who continued to meet the eligibility criteria were randomized to receive a sequence consisting of 2 study treatments, each administered for 12 weeks separated by a 14-day Washout Period. A total of 12 study clinic visits were conducted on an outpatient basis. The total duration of subject participation, including the Follow-up, was approximately 30 weeks. A total of 26 different sequences of 2 treatments were included. Potential treatment included UMEC/VI 125/25 mcg, UMEC/VI 62.5/25 mcg, UMEC 125 mcg, UMEC 62.5 mcg, VI 25 mcg and placebo. The sequences were selected to optimize power for the comparisons between the UMEC/VI doses and placebo and, therefore, the number of subjects receiving each treatment was unbalanced.

3.5.2. Enrollment Criteria

Study enrollment criteria were similar to the Primary Efficacy Studies (see Section 3.3.2) except that the Exercise/Lung Function Studies had an inclusion criterion for lung hyperinflation

defined by a resting FRC of ≥120% of predicted normal. This requirement was included to select subjects most likely to have exercise limitation, as hyperinflation is a significant factor in determining exercise capacity. Additionally, a lower limit was applied for post-albuterol FEV_1 (≥35% of predicted normal values) to preclude subjects with very severe disease from performing exercise tests.

3.5.3. Withdrawal Criteria

Similar to the Primary Efficacy Studies, subjects were to be withdrawn from the study if they experienced a clinically important laboratory or 12-lead ECG finding. Additionally, subjects were to be withdrawn from the study if they experienced a COPD exacerbation.

3.5.4. Assessments

The co-primary efficacy endpoints were EET postdose and trough FEV_1 at Week 12. The endurance shuttle walk test (ESWT) was used to evaluate EET. The ESWT is an exercise test to measure endurance capacity, which has been found to be sensitive to detecting changes in EET in COPD patients following bronchodilation [Pepin, 2005]. The MCID for the ESWT has been reported to be a change in EET of between 45 and 85 seconds [Pepin, 2011]). An incremental shuttle walk test (ISWT) was conducted during the Run-in Period to determine the walking speed at which subsequent ESWTs were conducted during the first Treatment Period. During the Washout Period, a further ISWT was used to reset the baseline for conduct of ESWTs during the second Treatment Period. Trough FEV_1 is defined as the mean of the FEV_1 value obtained at 23 and 24 hours after dosing.

Other assessments included measures of lung hyperinflation (inspiratory capacity, FRC, residual volume), 3-hour postdose FEV_1, rescue use, and ease of use of ELLIPTA DPI (both Exercise/Lung Function Studies) and exercise inspiratory capacity and cardiorespiratory measures (study 417 only). These assessments are not discussed in this briefing document.

Safety assessments included AE reporting, routine clinical laboratory assessments, evaluation of vital signs, 12-lead ECG measurements, and evaluation of COPD exacerbations.

3.5.5. Statistical Methods

3.5.5.1. Description of Analysis Populations

The ITT Population defined for the Primary Efficacy Studies (Section 3.3.6.1) is the population of primary interest for the Exercise/Lung Function Studies.

3.5.5.2. Treatment Comparisons

For each study, the primary treatment comparisons were:

- 3-hour postdose EET for UMEC/VI 125/25 mcg vs. placebo,
- Trough FEV_1 for UMEC/VI 125/25 mcg vs. placebo,
- 3-hour postdose EET for UMEC/VI 62.5/25 mcg vs. placebo, and

- Trough FEV_1 for UMEC/VI 62.5/25 mcg vs. placebo.

The comparison of each UMEC/VI dose with placebo was performed for each co-primary, secondary, and other efficacy endpoint for the ITT population. In addition, comparisons between each dose of UMEC and VI with placebo and of the combination treatments with the individual components of the same dose were performed for each endpoint. No direct comparisons between UMEC and VI or between different doses of UMEC or different doses of the combination were made.

3.5.5.3. Multiple Comparisons and Multiplicity

Within each Exercise/Lung Function Study, to account for multiplicity across the treatment comparisons for the co-primary endpoints, a step-down closed testing procedure was applied, whereby inference for a test in the pre-defined hierarchy was dependent upon statistical significance having been achieved for the previous tests in the hierarchy. If at any point in the hierarchy a comparison did not demonstrate statistical significance, all further statistical analyses were fully described but were not inferential. If statistical significance was achieved for all comparisons in the hierarchy, inference is drawn from all other treatment comparisons in the study with no adjustment for multiplicity. The hierarchy consisted of the primary treatment comparisons identified in Section 3.5.5.2, performed in that order.

Statistical significance was achieved at all points in the hierarchy for one of the Exercise/Lung Function Studies (study 418). In the other Exercise/Lung Function Study (study 417), statistical significance was not achieved for the first treatment comparison in the hierarchy and so further results cannot be considered inferential according to the strict terms of the hierarchy. The results from both studies were reported in their entirety (i.e., treatment difference, LS means, 95% CIs and p-values), with notations when inference could not be made based on failure of a prior test in the hierarchy.

3.5.5.4. Co-primary Efficacy Analyses

The co-primary endpoint of 3 hour post-dose EET at Week 12 was analyzed using an MMRM analysis, including covariates of period walking speed, mean walking speed, period, treatment, visit, smoking status, center group, visit by period walking speed interaction, visit by mean walking speed interaction and visit by treatment interaction, where visit is nominal.

The co-primary endpoint of trough FEV_1 at Week 12 was analyzed using an MMRM analysis, including covariates of period baseline, mean baseline, period, treatment, visit, smoking status, center group, visit by period baseline interaction, visit by mean baseline interaction and visit by treatment interaction, where visit is nominal. The models used all available values recorded on Day 2, Week 6 and Week 12. Missing data were not directly imputed in this analysis; however, all non-missing data for a subject were used within the analysis to estimate the treatment effect at Week 12. The impact of missing data on the efficacy conclusions was investigated using sensitivity analysis following multiple imputation in a similar way to that described for the Primary Efficacy Studies in Section 10.3.2. Imputation was performed in each treatment period separately.

4. CLINICAL EFFICACY

4.1. Overview of Clinical Efficacy

Key features of the 7 Phase III studies designed to evaluate the efficacy and safety of UMEC/VI and the individual components are provided in Section 1.4, Table 2.

4.2. Primary Efficacy Studies

4.2.1. Subject Disposition

Summary findings for subject disposition are presented from the integration of data for the 4 Primary Efficacy Studies in Table 24. The integrated data is representative of that from the individual studies. At least 70% of subjects in each treatment group completed the study. The most common reasons for withdrawal were lack of efficacy and AE.

Table 24 Overall Subject Disposition (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

	Number (%) of Subjects							
	Placebo N=555	UMEC/VI 62.5/25 N=837	UMEC/VI 125/25 N=826	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1030	TIO N=418	Total N=4713
Completion Status								
Completed [a]	387 (70)	672 (80)	659 (80)	324 (78)	477 (76)	779 (76)	349 (83)	3647 (77)
Withdrawn	168 (30)	165 (20)	167 (20)	94 (22)	152 (24)	251 (24)	69 (17)	1066 (23)
Primary Reason/Subreason for Withdrawal [b]								
Adverse event	26 (5)	53 (6)	47 (6)	34 (8)	41 (7)	59 (6)	20 (5)	280 (6)
Lack of efficacy	81 (15)	41 (5)	38 (5)	20 (5)	60 (10)	85 (8)	19 (5)	344 (7)
Exacerbation	60 (11)	35 (4)	33 (4)	18 (4)	46 (7)	70 (7)	15 (4)	277 (6)
Protocol deviation	8 (1)	11 (1)	13 (2)	7 (2)	4 (<1)	22 (2)	1 (<1)	66 (1)
Subject reached protocol-defined stopping criteria	25 (5)	26 (3)	34 (4)	13 (3)	22 (3)	40 (4)	11 (3)	171 (4)
ECG abnormality	16 (3)	23 (3)	32 (4)	7 (2)	14 (2)	30 (3)	11 (3)	133 (3)
Lab abnormality	0	0	0	2 (<1)	0	2 (<1)	0	4 (<1)
Holter abnormality	9 (2)	3 (<1)	2 (<1)	4 (<1)	8 (1)	9 (<1)	0	35 (<1)
Study closed/terminated	0	0	0	0	0	0	0	0
Lost to follow-up	1 (<1)	3 (<1)	4 (<1)	0	2 (<1)	5 (<1)	3 (<1)	18 (<1)
Withdrew consent	27 (5)	31 (4)	31 (4)	20 (5)	23 (4)	40 (4)	15 (4)	187 (4)
Subject relocated	3 (<1)	3 (<1)	5 (<1)	2 (<1)	1 (<1)	6 (<1)	0	20 (<1)
Frequency of visits	5 (<1)	3 (<1)	6 (<1)	1 (<1)	0	7 (<1)	2 (<1)	24 (<1)
Burden of procedures	4 (<1)	4 (<1)	4 (<1)	4 (<1)	4 (<1)	4 (<1)	5 (1)	29 (<1)
Other	8 (1)	19 (2)	14 (2)	10 (2)	15 (2)	16 (2)	8 (2)	90 (2)

Abbreviations: ECG=electrocardiogram; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

a. Subjects were considered to have completed if they completed the last clinic visit (Visit 9) and did not withdraw at that visit.

b. Subjects only recorded 1 primary reason for withdrawal. Subjects were not required to indicate a sub-reason for all primary reasons; however, if they did, they could mark more than 1 if appropriate.

4.2.2. Demographic and Baseline Characteristics

Summary findings for demographic characteristics of subjects are presented from the integration of data for the 4 Primary Efficacy Studies in Table 25. The integrated data are representative of that from the individual studies. The mean age was 63.3 years and more males than females were enrolled. The predominant race category was White. Overall, 3% of subjects were of African Heritage/African American. In the US, approximately 10% of subjects were African American.

Table 25 Summary of Demographic Characteristics (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

Demographic Characteristic	Placebo N=555	UMEC/VI 62.5/25 N=837	UMEC/VI 125/25 N=826	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1030	TIO N=418	Total N=4713
Age (years), n	555	837	826	418	629	1030	418	4713
Mean	62.2	63.6	63.4	64.0	63.6	62.9	64.1	63.3
SD	8.79	8.67	8.40	9.16	8.45	8.73	8.87	8.70
Min, Max	40, 86	40, 86	40, 84	40, 93	40, 86	40, 88	41, 88	40, 93
Sex, n	555	837	826	418	629	1030	418	4713
Female, n (%)	185 (33)	246 (29)	268 (32)	120 (29)	211 (34)	340 (33)	127 (30)	1497 (32)
Male, n (%)	370 (67)	591 (71)	558 (68)	298 (71)	418 (66)	690 (67)	291 (70)	3216 (68)
Race, n	555	837	826	418	629	1030	418	4713
White, n (%)	475 (86)	689 (82)	694 (84)	354 (85)	533 (85)	898 (87)	336 (80)	3979 (84)
African Heritage/ African American, n (%)	18 (3)	29 (3)	21 (3)	14 (3)	10 (2)	19 (2)	14 (3)	125 (3)
Asian, n (%)	49 (9)	73 (9)	77 (9)	35 (8)	77 (12)	76 (7)	38 (9)	425 (9)
Other, n (%)	13 (2)	46 (5)	34 (4)	15 (4)	9 (1)	37 (3)	30 (7)	184 (4)
Body Mass Index (kg/m^2), n	555	837	825	418	629	1029	418	4711
Mean	26.70	27.12	26.48	26.46	26.42	26.99	26.89	26.76
SD	6.003	5.994	5.291	5.595	5.791	5.917	5.696	5.774
Min, Max	12.3, 50.7	14.5, 54.6	13.9, 52.5	14.5, 47.1	14.4, 56.7	13.3, 48.3	15.1, 53.2	12.3, 56.7

Abbreviations: Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Summary findings for baseline COPD and lung function characteristics are presented from the integration of data for the 4 Primary Efficacy Studies in Table 26. The integrated data are representative of that from the individual studies. Approximately half (49%) of the subjects were current smokers and approximately half (49%) were using concurrent ICS therapy. The majority of subjects had moderate to very severe COPD based on baseline percent predicted FEV_1 values. Thirty-one percent of subjects were reversible to albuterol (defined as an increase in FEV_1 of $\geq$12% and $\geq$200 mL following administration of 4 puffs of albuterol). The majority of subjects (72%) did not report a COPD exacerbation requiring oral corticosteroids or antibiotics in the year prior to screening.

Table 26 Summary of Baseline COPD and Lung Function Characteristics (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

Parameter	Placebo N=555	UMEC/VI 62.5/25 N=837	UMEC/VI 125/25 N=826	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1030	TIO N=418	Total N=4713
Years smoked, n	555	837	826	418	629	1030	418	4713
Mean (SD)	38.5	38.5	38.4	39.1	39.7	37.7	38.2	38.5
Min, Max	8, 67	8, 67	7, 69	6, 75	8, 66	10, 68	5, 65	5, 75
Smoking pack-years,n	555	837	826	418	629	1030	418	4713
Mean (SD)	45.4	46.3	45.0	46.8	45.3	43.1	47.9	45.3
Min, Max	10, 185	10, 250	3, 225	10, 225	10, 190	10, 175	10, 265	3, 265
Smoking status at Screening, n	555	837	826	418	629	1030	418	4713
Current smoker, n (%)	293 (53)	390 (47)	415 (50)	207 (50)	314 (50)	511 (50)	196 (47)	2326 (49)
Former smoker, n (%)	262 (47)	447 (53)	411 (50)	211 (50)	315 (50)	519 (50)	222 (53)	2387 (51)
Post-albuterol FEV_1 (L), n	554	834	821	417	627	1024	415	4692
Mean	1.378	1.401	1.392	1.347	1.400	1.425	1.367	1.394
SD	0.4662	0.5136	0.4658	0.4730	0.4969	0.4999	0.4694	0.4875
Post-albuterol FEV_1/FVC (%), n	554	834	821	417	627	1024	415	4692
Mean	46.759	47.417	46.380	46.775	46.379	47.417	46.878	46.914
SD	11.3812	11.4116	11.0132	11.0696	10.8955	11.2647	11.7713	11.2427
Post-albuterol Percent Predicted FEV_1 (%), n	554	834	821	417	627	1024	415	4692
Mean	47.1	47.8	47.4	46.8	47.9	48.3	47.5	47.7
SD	12.59	13.19	12.69	13.39	12.62	12.94	13.22	12.92
Reversibility to Albuterol [a], n	553	834	821	415	625	1022	412	4682
Not Reversible, n (%)	385 (70)	586 (70)	549 (67)	294 (71)	418 (67)	697 (68)	306 (74)	3235 (69)
Reversibile, n (%)	168 (30)	248 (30)	272 (33)	121 (29)	207 (33)	325 (32)	106 (26)	1447 (31)
ICS use at Screening, n	555	837	826	418	629	1030	418	4713
ICS user, n (%)	275 (50)	408 (49)	389 (47)	219 (52)	317 (50)	485 (47)	208 (50)	2301 (49)
ICS non-user, n (%)	280 (50)	429 (51)	437 (53)	199 (48)	312 (50)	545 (53)	210 (50)	2412 (51)
GOLD stage, n	554	834	821	417	627	1024	415	4692
I: $FEV_1 \geq 80\%$ predicted	0	0	0	0	0	0	0	0
II: $50\% \leq FEV_1 < 80\%$ predicted	240 (43)	409 (49)	362 (44)	191 (46)	280 (45)	498 (49)	195 (47)	2175 (46)
III: $30\% \leq FEV_1 < 50\%$ predicted	265 (48)	331 (40)	375 (46)	172 (41)	286 (46)	425 (42)	169 (41)	2023 (43)
IV: $FEV_1 < 30\%$ predicted	49 (9)	94 (11)	84 (10)	54 (13)	61 (10)	101 (10)	51 (12)	494 (11)
COPD type, n	552	836	825	418	625	1029	417	4702
Chronic bronchitis, n (%)	381 (69)	561 (67)	550 (67)	274 (66)	386 (62)	678 (66)	266 (64)	3096 (66)
Emphysema, n (%)	333 (60)	487 (58)	487 (59)	271 (65)	363 (63)	617 (60)	257 (62)	2845 (61)
COPD Exacerbations in Previous Year, n	555	837	826	418	629	1030	418	4713
Requiring oral steroids or antibiotics, n (%)								
0	410 (74)	615 (73)	579 (70)	298 (71)	473 (75)	751 (73)	283 (68)	3409 (72)
≥1	145 (26)	222 (27)	247 (30)	120 (29)	156 (25)	279 (27)	135 (32)	1304 (28)
Requiring hospitalization, n (%)								
0	500 (90)	759 (91)	756 (92)	367 (88)	584 (93)	903 (88)	366 (88)	4235 (90)
≥1	55 (10)	78 (9)	70 (8)	51 (12)	45 (7)	127 (12)	52 (12)	478 (10)

Abbreviations: COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; GOLD=Global Initiative for Obstructive Lung Disease; ICS=inhaled corticosteroid; Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

a. Defined as an improvement in FEV_1 following administration of a short-acting bronchodilator of ≥12% and ≥200 mL from pre-treatment levels

4.2.3. Lung Function: Placebo-controlled Studies 373 and 361

4.2.3.1. Primary Endpoint: Trough FEV_1 at Day 169 (Week 24)

Both doses of UMEC/VI (62.5/25 and 125/25 mcg) and the UMEC (62.5 and 125 mcg) and VI 25 mcg monotherapies demonstrated statistically significant and clinically meaningful increases in trough FEV_1 at Day 169 compared with placebo (Table 27 and Figure 16).

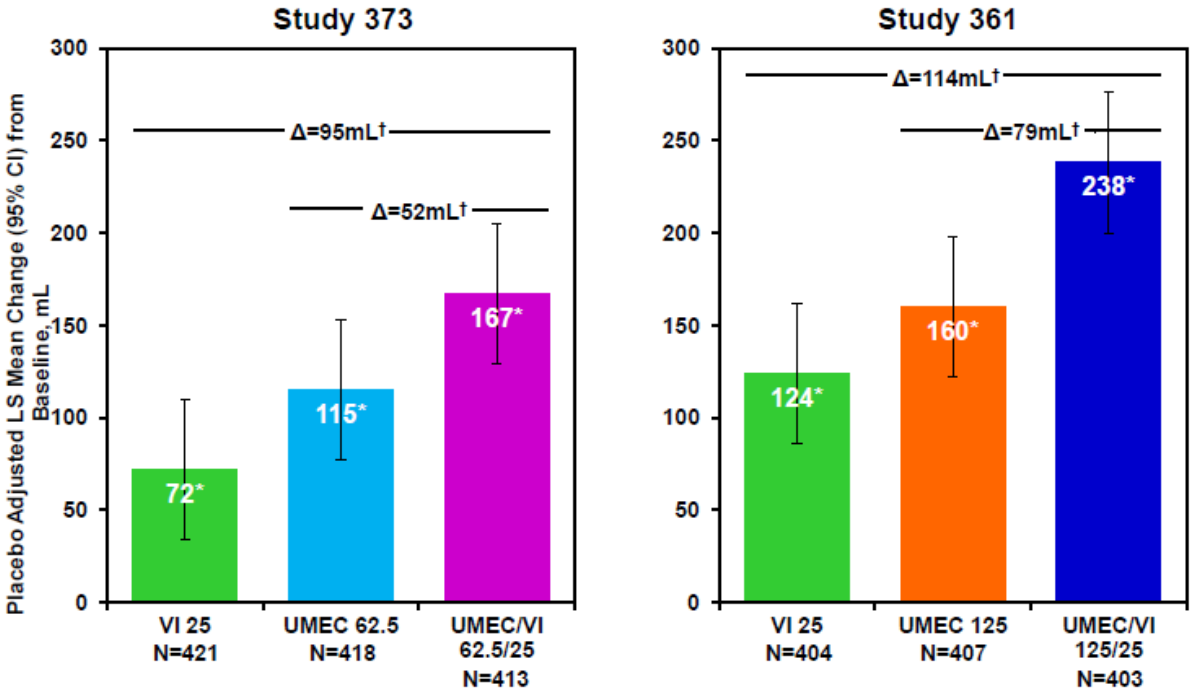
For comparisons with components, both doses of UMEC/VI (62.5/25 and 125/25 mcg) demonstrated statistically significant and clinically meaningful increases in trough FEV_1 at Day 169 compared with respective component doses of UMEC (62.5 and 125 mcg) and VI 25 mcg, confirming that both of the components contribute to efficacy of the UMEC/VI combination at the end of the dosing interval.

Table 27 Primary Efficacy Analysis: Trough FEV_1 (mL) at Day 169 (Studies 373 and 361)

Study 373	Placebo N=280	UMEC 62.5 N=418	VI 25 N=421	UMEC/VI 62.5/25 N=413
LS mean (SE) LS mean change from baseline (SE)	1239 (15.8) 4 (15.8)	1354 (12.6) 119 (12.6)	1311 (12.7) 76 (12.7)	1406 (12.6) 171 (12.6)
Difference vs. Placebo 95% CI p-value		115 (76,155) <0.001	72 (32,112) <0.001	167 (128,207) <0.001
UMEC/VI vs. VI 95% CI p-value				95 (60,130) <0.001
UMEC/VI vs. UMEC 62.5 95% CI p-value				52 (17,87) 0.004
Study 361	Placebo N=275	UMEC 125 N=407	VI 25 N=404	UMEC/VI 125/25 N=403
LS mean (SE) LS mean change from baseline (SE)	1245 (15.3) -31 (15.3)	1405 (11.9) 129 (11.9)	1370 (12.1) 93 (12.1)	1484 (11.9) 207 (11.9)
Difference vs. Placebo 95% CI p-value		160 (122,198) <0.001	124 (86,162) <0.001	238 (200,276) <0.001
UMEC/VI vs. VI 95% CI p-value				114 (81,148) <0.001
UMEC/VI vs. UMEC 125 95% CI p-value				79 (46,112) <0.001

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol

Figure 16 Placebo-Adjusted LS Mean Change from Baseline for Trough FEV_1 (mL) at Day 169 (Studies 373 and 361)



*p<0.001 vs. placebo
† p≤0.004 for UMEC/VI 62.5/25 vs. UMEC 62.5 and VI and for UMEC/VI 125/25 vs. UMEC 125 and VI 25

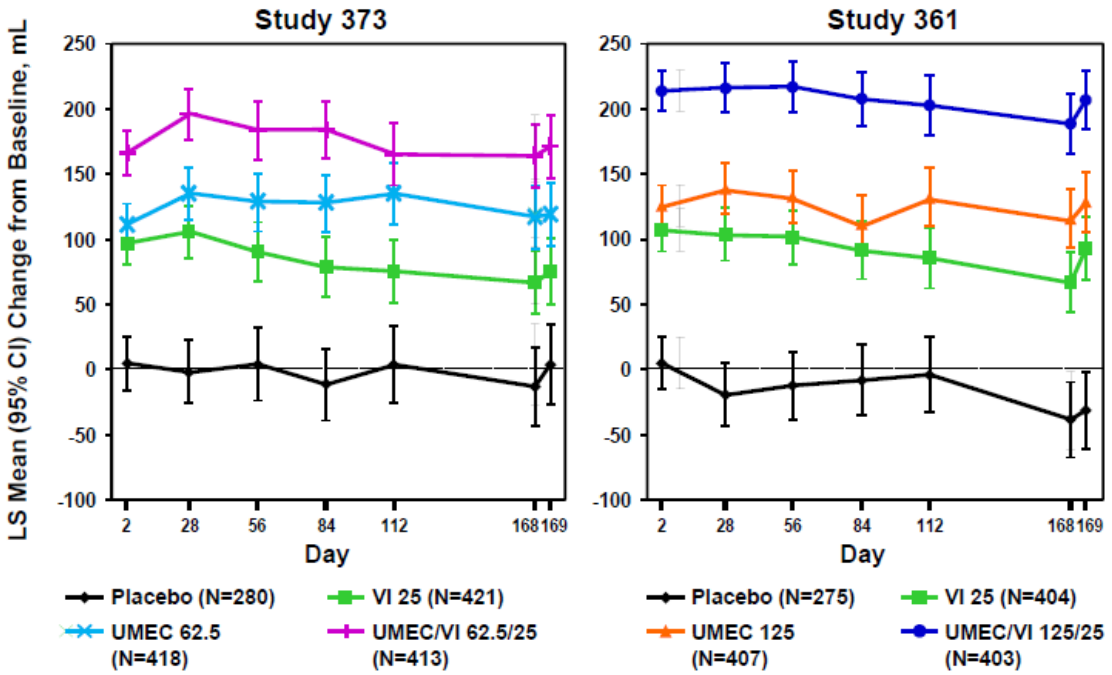
Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol

4.2.3.2. Trough FEV_1 over 24 Weeks

Beginning at Day 2 and continuing throughout the study, UMEC/VI (62.5/25 and 125/25 mcg), UMEC (62.5 and 125 mcg) and VI 25 mcg demonstrated statistically significant increases in trough FEV_1 compared with placebo (Figure 17).

For comparisons with components, both doses of UMEC/VI (62.5/25 and 125/25 mcg) exhibited statistically significant increases in trough FEV_1 at all assessments throughout the study compared with respective component doses of UMEC (62.5 and 125 mcg) and VI 25 mcg, except for UMEC/VI 62.5/25 mcg vs. UMEC 62.5 mcg at Day 112 (Figure 17). This demonstrates the efficacy of both doses of UMEC/VI at the end of the 24-hour dosing interval.

Figure 17: LS Mean Change from Baseline for Trough FEV_1 (mL) over 24 Weeks (Studies 373 and 361)



p<0.001 for all comparisons of UMEC/VI (62.5/25 and 125/25), UMEC (62.5 and 125), VI with placebo
p≤0.006 for all comparisons of UMEC/VI (62.5/25 and 125/25) with monotherapies, except UMEC/VI 62.5/25 vs UMEC 62.5 at Day 112 (p=0.076)

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; UMEC=umeclidinium bromide; VI=vilanterol

4.2.3.3. Secondary Endpoint: 0 to 6 hour Weighted Mean FEV_1 at Day 168 (Week 24)

Both doses of UMEC/VI (62.5/25 and 125/25 mcg) and the UMEC (62.5 and 125 mcg) and VI 25 mcg monotherapies demonstrated statistically significant increases in 0 to 6 hour weighted mean FEV_1 at Day 168 compared with placebo (Table 28 and Figure 18).

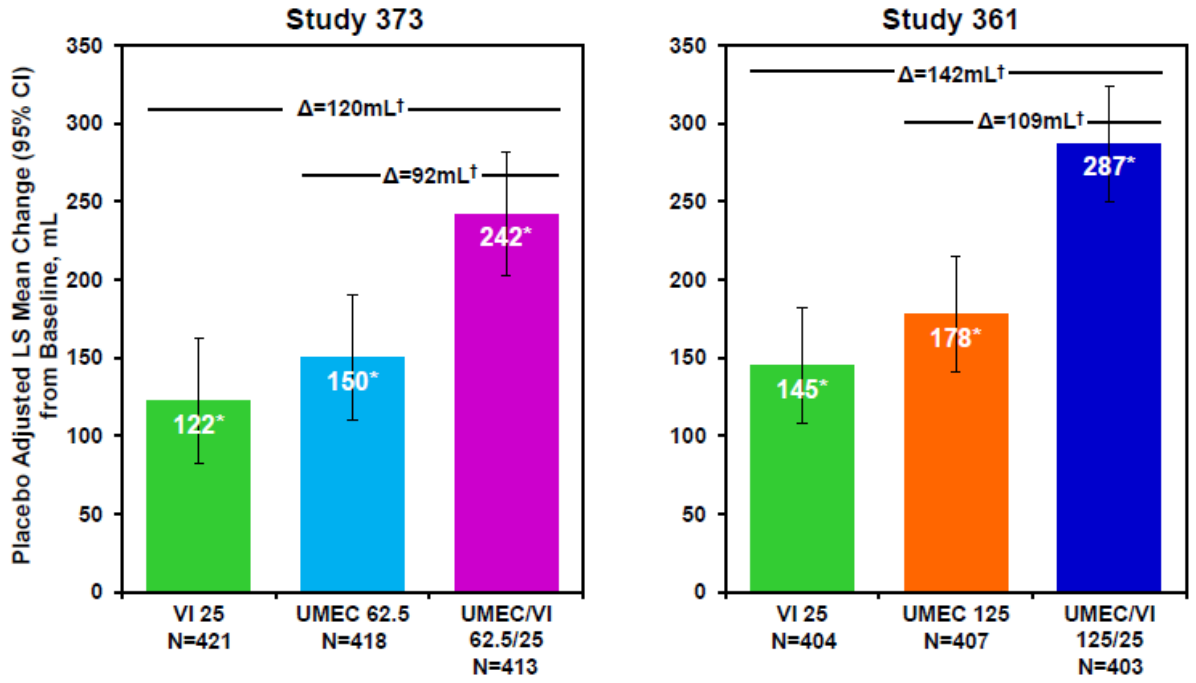
For comparisons with components, both doses of UMEC/VI (62.5/25 and 125/25 mcg) demonstrated statistically significant increases in 0 to 6 hour weighted mean FEV_1 at Day 168 compared with respective component doses of UMEC (62.5 and 125 mcg) and VI 25 mcg, confirming that both of the components contribute to efficacy of the UMEC/VI combination over the initial portion of the dosing interval and providing additional evidence for the contribution of UMEC and VI to the combination.

Table 28 Secondary Efficacy Analysis: 0 to 6 hour Weighted Mean FEV_1 (mL) at Day 168 (Studies 373 and 361)

Study 373	Placebo N=280	UMEC 62.5 N=418	VI 25 N=421	UMEC/VI 62.5/25 N=413
LS mean (SE) LS mean change from baseline (SE)	1237 (15.8) 1 (15.8)	1387 (12.8) 151 (12.8)	1359 (12.8) 123 (12.8)	1479 (12.7) 243 (12.7)
Difference vs. Placebo 95% CI p-value		150 (110,190) <0.001	122 (82,162) <0.001	242 (202, 282) <0.001
UMEC/VI vs. VI 95% CI p-value				120 (84,155) <0.001
UMEC/VI vs. UMEC 62.5 95% CI p-value				92 (56,127) <0.001
Study 361	Placebo N=275	UMEC 125 N=407	VI 25 N=404	UMEC/VI 125/25 N=403
LS mean (SE) LS mean change from baseline (SE)	1257 (15.0) -18 (15.0)	1435 (11.8) 160 (11.8)	1402 (11.9) 127 (11.9)	1544 (11.8) 269 (11.8)
Difference vs. Placebo 95% CI p-value		178 (141,216) <0.001	145 (107,182) <0.001	287 (250,324) <0.001
UMEC/VI vs. VI 95% CI p-value				142 (109,175) <0.001
UMEC/VI vs. UMEC 125 95% CI p-value				109 (76,141) <0.001

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol

Figure 18 Placebo-Adjusted LS Mean Change from Baseline for 0 to 6 hour Weighted Mean FEV_1 (mL) at Day 168 (Studies 373 and 361)



*p<0.001 vs. placebo

† p<0.001 for UMEC/VI 62.5/25 vs. UMEC 62.5 and VI and for UMEC/VI 125/25 vs. UMEC 125 and VI 25

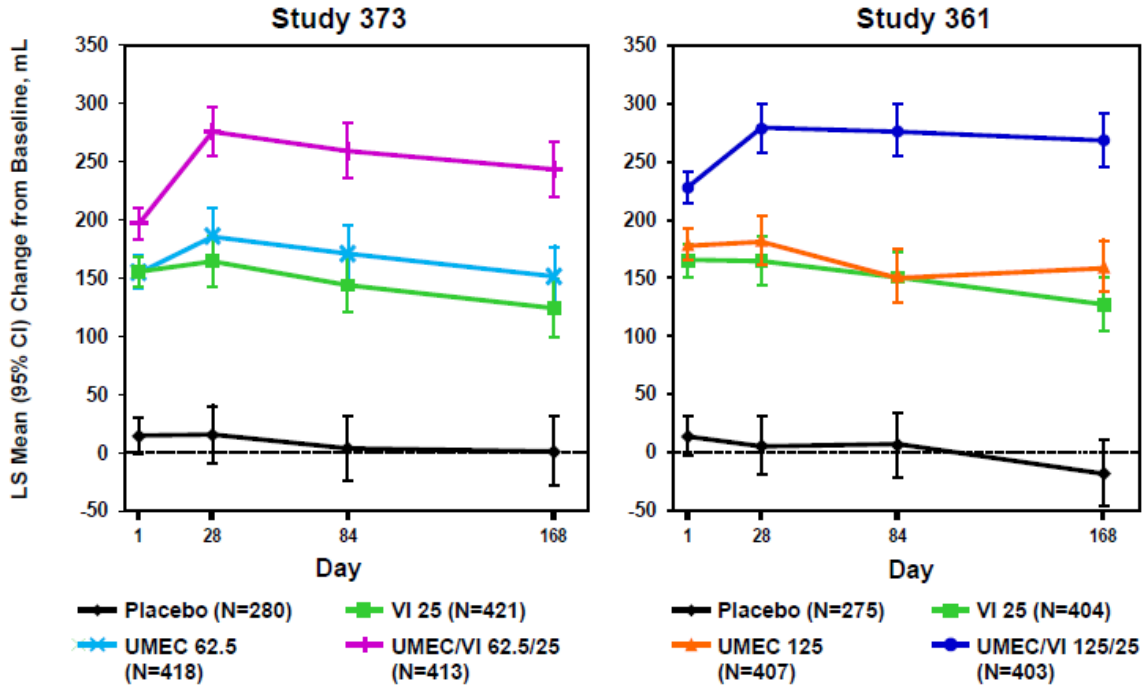
Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol

4.2.3.4. 0 to 6 hour Weighted Mean FEV_1 over 24 Weeks

Beginning at Day 28 and continuing throughout the study, UMEC/VI (62.5/25 and 125/25 mcg), UMEC (62.5 and 125 mcg) and VI 25 mcg demonstrated statistically significant increases in 0 to 6 hour weighted mean FEV_1 compared with placebo (Figure 19).

For comparisons with components, both doses of UMEC/VI (62.5/25 and 125/25 mcg) demonstrated statistically significant increases in 0 to 6 hour weighted mean FEV_1 at all assessments throughout the study compared with respective component doses of UMEC (62.5 and 125 mcg) and VI 25 mcg. This demonstrates the efficacy of both doses of UMEC/VI over the initial part of the dosing interval.

Figure 19 LS Mean Change from Baseline for 0 to 6 hour Weighted Mean FEV_1 (mL) over 24 Weeks (Studies 373 and 361)



p<0.001 for all comparisons of UMEC/VI (62.5/25 and 125/25), UMEC (62.5 and 125), VI with placebo
P<0.001 for all comparisons of UMEC/VI (62.5/25 and 125/25) with monotherapies

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; UMEC=umeclidinium bromide; VI=vilanterol

4.2.3.5. Serial FEV_1 (All Subjects): Onset of Effect

After the first dose of study medication (Day 1), both doses of UMEC/VI (62.5/25 and UMEC/VI 125/25 mcg) resulted in a statistically significant increase in FEV_1 compared with placebo at the first serial assessment (15 minutes post-dose: $p<0.001$) and at all subsequent timepoints (30 minutes and 1, 3, and 6 hours).

Similar results were obtained at Days 28, 84, and 168. For both doses, statistically significant increases were consistently observed for the UMEC/VI doses over component monotherapies after 3 hours at Day 1, and at all serial timepoints on Day 28, Day 84, and Day 168.

4.2.3.6. Serial FEV_1 over 0 to 24 Hours Postdose (TFH Subset)

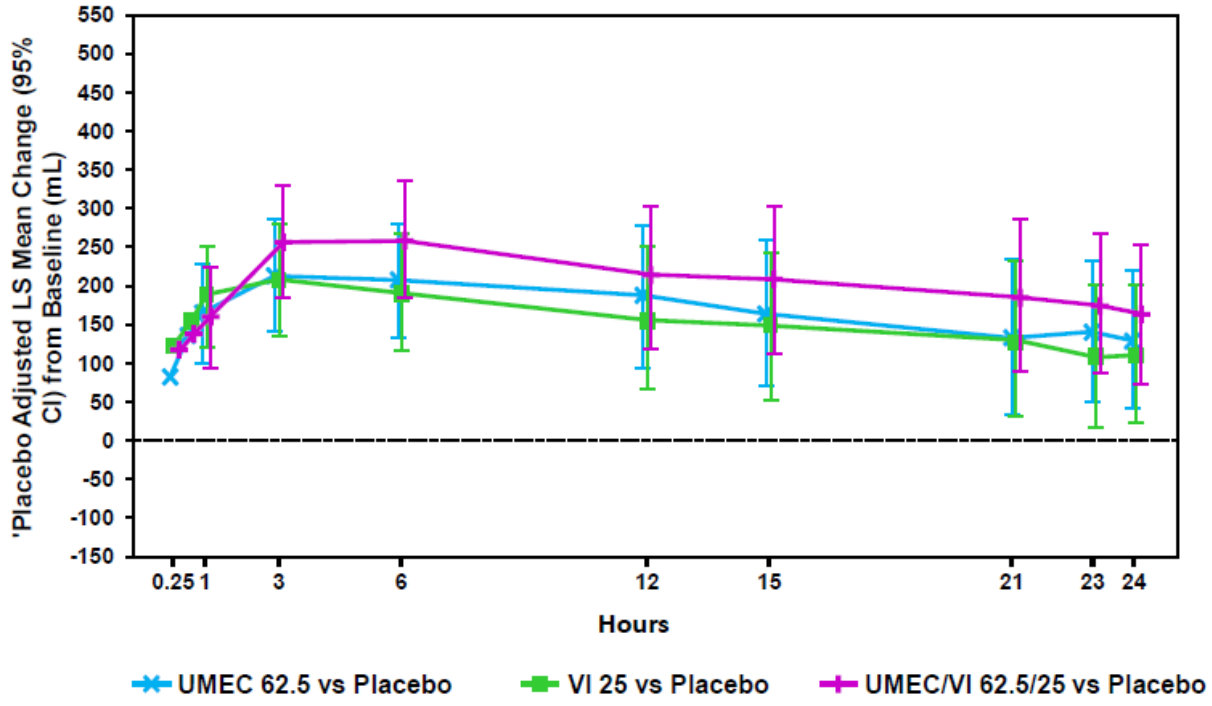
Comprehensive 24-hour serial spirometry measurements were obtained to evaluate lung function over the entire dosing period in the TFH subset of the placebo-controlled Primary Efficacy Studies (n=197 in study 373 and n=199 in study 361).

The 24-hour serial spirometry profiles on Days 1 and 168 showed treatment with UMEC/VI 62.5/25 and UMEC/VI 125/25 mcg and their respective components resulted in sustained

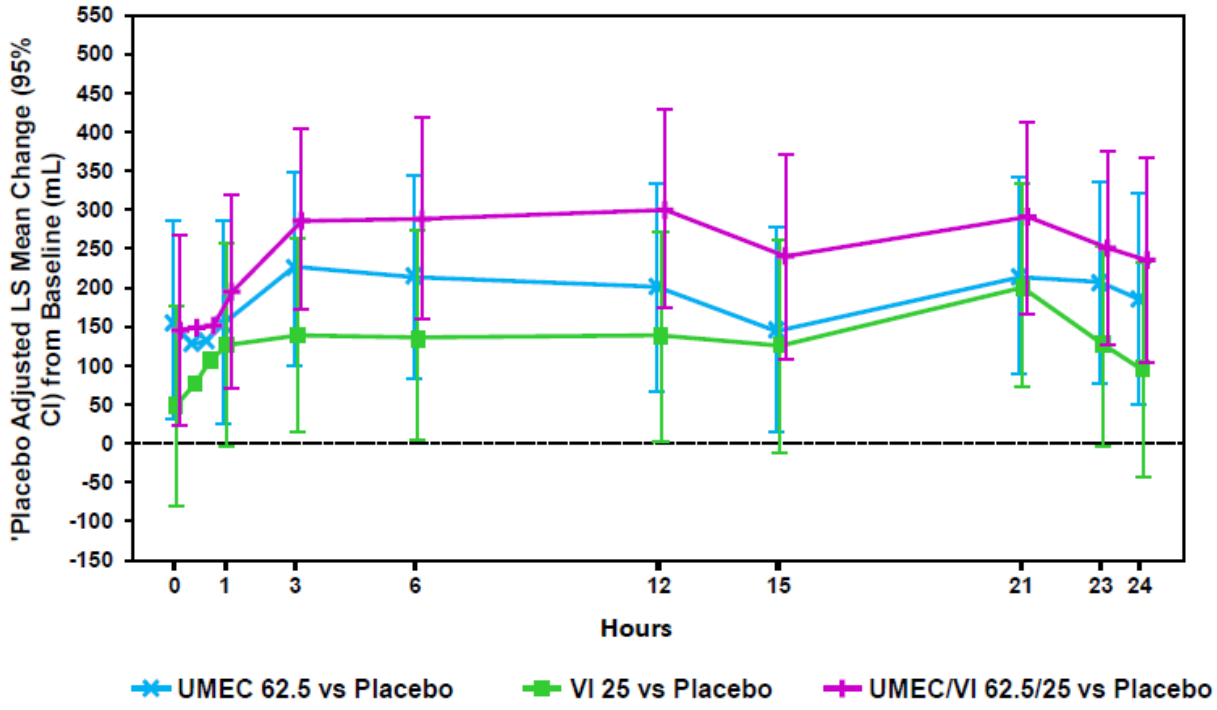
improvements in lung function over 24 hours compared with placebo (Figure 20). Postdose increases in FEV_1 were numerically greater for each dose of UMEC/VI compared with its respective components at almost all time points, with the exception of some of the earliest time points on Day 1.

Figure 20 Placebo-Adjusted LS Mean Change from Baseline in FEV_1 (L) Over Time (0 to 24 hour) on Days 1 and 168 (Subset of Individual Studies 361 and 373)

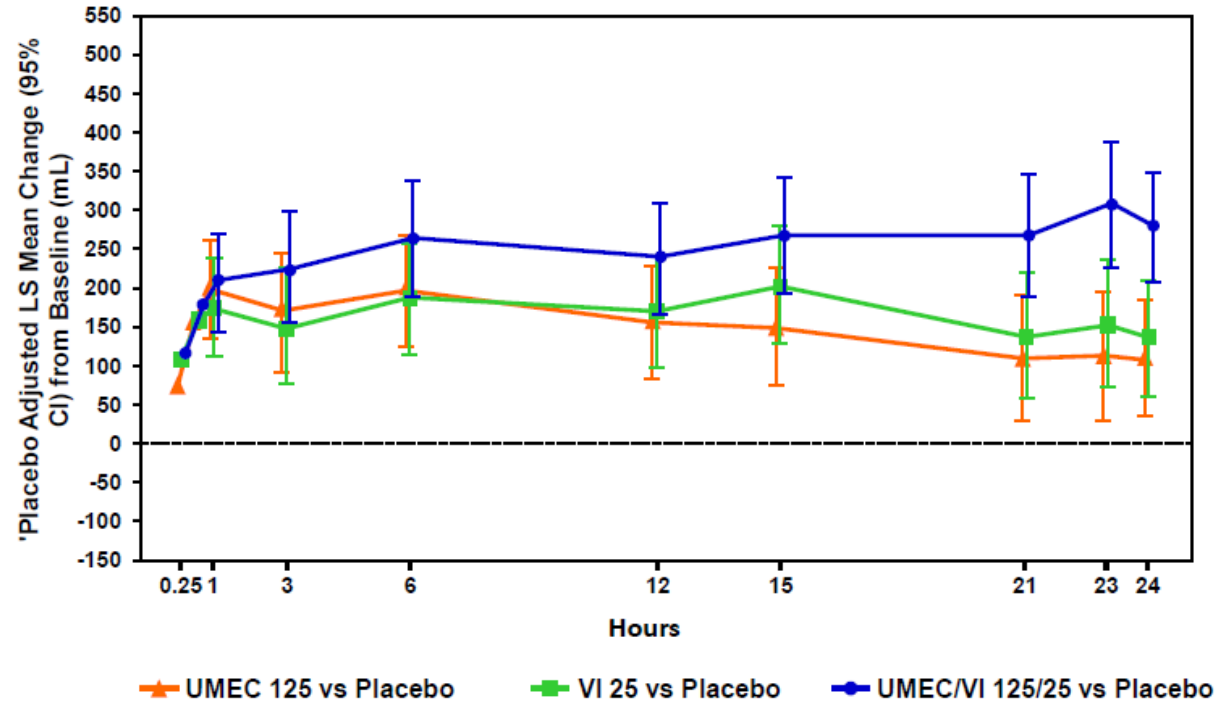
Study 373: Day 1



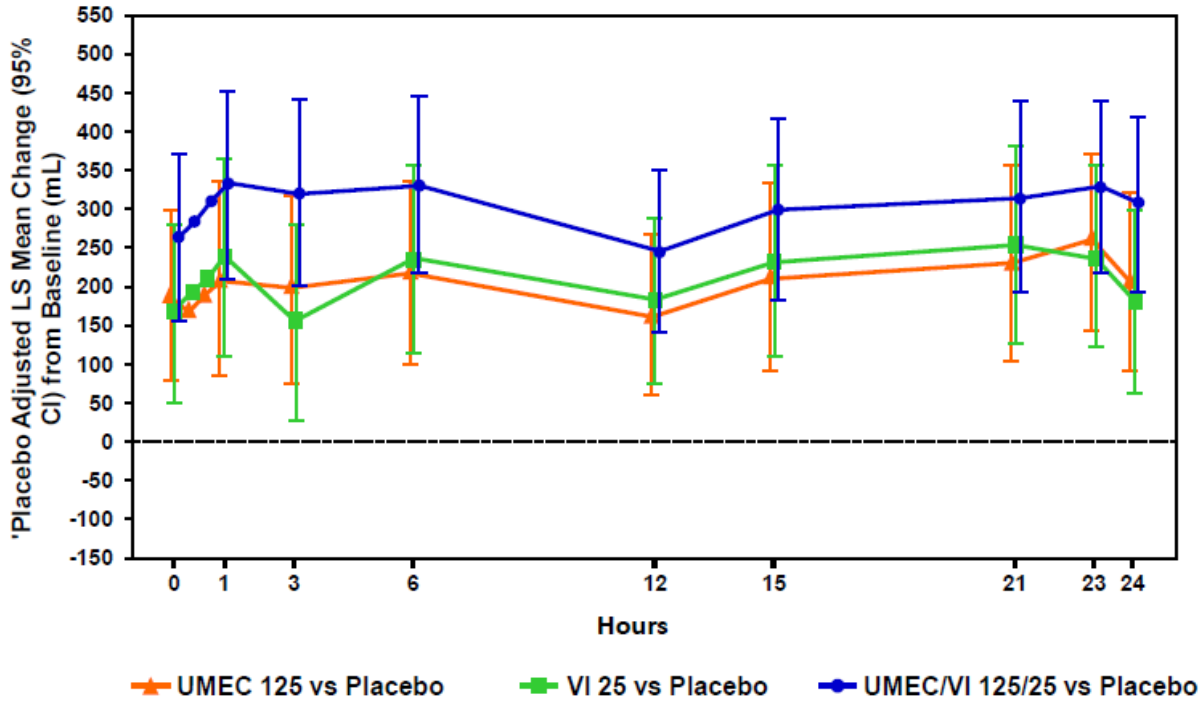
Study 373: Day 168



Study 361: Day 1



Study 361: Day 168



Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; TFH=twenty-four hour; UMEC=umeclidinium bromide; VI=vilanterol

4.2.4. Lung Function: Active-comparator Studies 360 and 374

4.2.4.1. Primary Endpoint: Trough FEV_1 at Day 169 (Week 24)

In study 360, statistically significant increases in trough FEV_1 at Day 169 (Week 24) were demonstrated for comparisons of UMEC/VI 62.5/25 and 125/25 mcg with VI 25 mcg (Table 29 and Figure 21), further demonstrating the contribution of UMEC to the combination. In study 374, the comparison of 125/25 mcg with UMEC 125 mcg for trough FEV_1 at Week 24 was not statistically significant. The finding for the comparison of UMEC/VI 125/25 mcg with UMEC 125 mcg is in contrast to that reported for placebo-controlled study 361 which showed a statistically significant difference for the comparison (Section 4.2.3.1).

In both active-comparator studies, all comparisons of UMEC/VI 62.5/25 mcg and 125/25 mcg with tiotropium for trough FEV_1 at Day 169 achieved p-values of <0.05. Improvements in trough FEV_1 for UMEC/VI 125/25 mcg compared to tiotropium were statistically significant in both studies and improvements in trough FEV_1 for UMEC/VI 62.5/25 mcg were statisticially significant in study 361 (see Section 4.2.3.1 for study 361). In study 374, the p-value for the comparison of UMEC/VI 62.5/25 mcg with tiotropium is nominal as a prior test in the predefined testing hierarchy (the comparison of UMEC/VI 125/25 mcg with UMEC 125 mcg for

trough FEV_1 at Week 24) did not achieve statistical significance. The improvements were comparable for the 2 UMEC/VI doses.

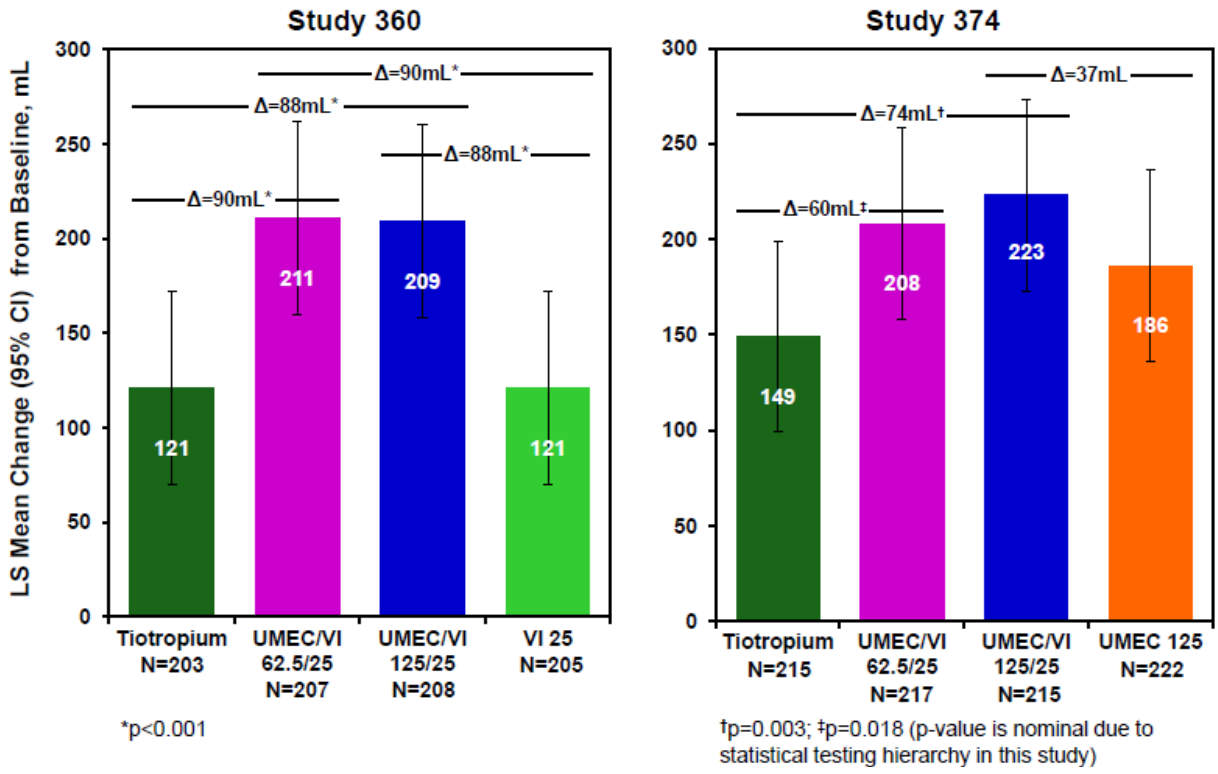
Table 29 Primary Efficacy Analysis: Trough FEV_1 (mL) at Day 169 (Studies 360 and 374)

DB2113360	VI 25 N=205	UMEC/VI 62.5/25 N=207	UMEC/VI 125/25 N=208	TIO N=203
LS mean (SE) LS mean change from baseline(SE)	1431 (18.9) 121 (18.9)	1521 (18.3) 211 (18.3)	1519 (18.7) 209 (18.7)	1431 (18.6) 121 (18.6)
UMEC/VI vs. VI 95% CI p-value		90 (39,142) <0.001	88 (36,140) <0.001	
UMEC/VI vs. tiotropium 95% CI p-value		90 (39,141) <0.001	88 (36,140) <0.001	
DB2113374	UMEC 125 N=222	UMEC/VI 62.5/25 N=217	UMEC/VI 125/25 N=215	TIO N=215
LS mean (SE) LS mean change from baseline (SE)	1332 (17.8) 186 (17.8)	1355 (18.0) 208 (18.0)	1369 (17.9) 223 (17.9)	1295 (17.6) 149 (17.6)
Difference vs. UMEC 125 95% CI p-value		22 (-27, 72) 0.377	37 (-12, 87) 0.142	
UMEC/VI vs. tiotropium 95% CI p-value		60 (10, 109) 0.018 [a]	74 (25, 123) 0.003	

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

a. p-values are nominal for this comparison according to the terms of the testing hierarchy for study 374.

Figure 21 LS Mean Change from Baseline for Trough FEV_1 (mL) at Day 169 (Studies 360 and 374)



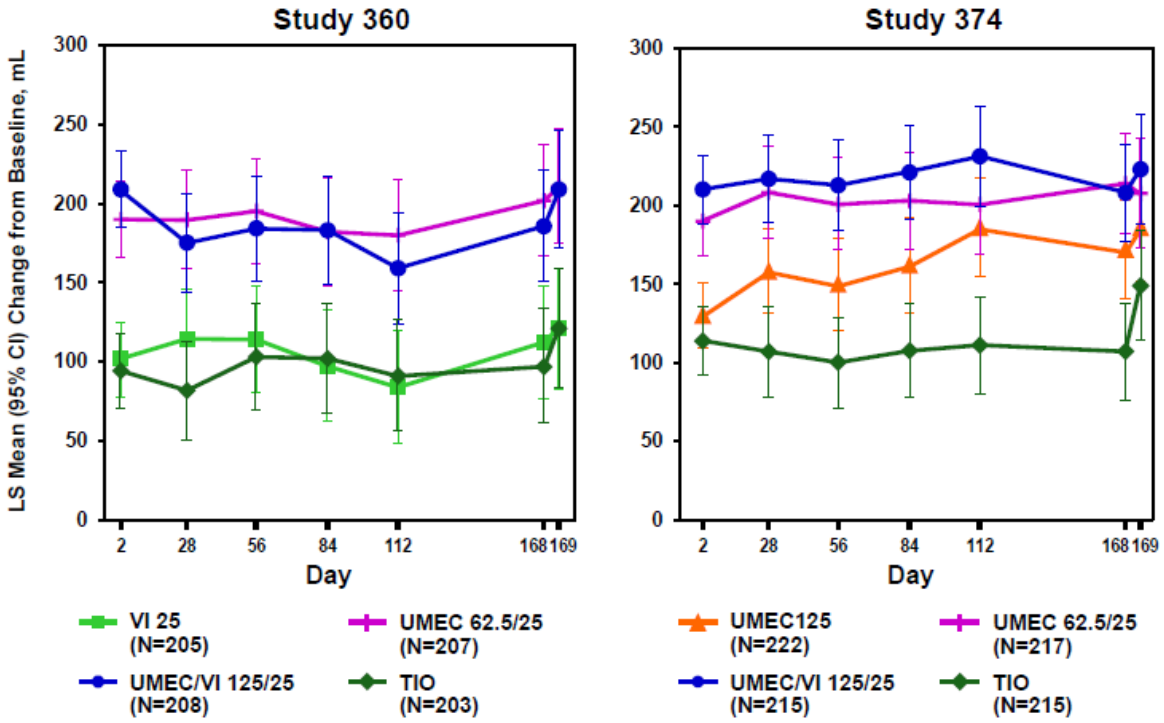
Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

4.2.4.2. Trough FEV_1 over 24 Weeks

Throughout the studies, both doses of UMEC/VI (62.5/25 and 125/25 mcg) showed mean increases in trough FEV_1 compared with tiotropium and VI 25 mcg (Figure 22).

For comparisons of UMEC/VI 125/25 mcg with UMEC 125 mcg, mean increases in trough FEV_1 were demonstrated for UMEC/VI 125/25 mcg at Day 2, 28, 56, and 84. At subsequent visits, differences between UMEC/VI 125/25 mcg and UMEC 125 mcg were not observed. Of note, an increase in the mean change from baseline for trough FEV_1 between Day 84 and Day 112 was observed in the UMEC 125 mcg group, while the increases from baseline in trough FEV_1 were generally consistent throughout the 24-week treatment period in the UMEC/VI 125/25 mcg group. The additional improvements in trough FEV_1 observed from Day 112 onwards in the UMEC 125 mcg group in this study were not evident in the UMEC 125 mcg group in study 361.

Figure 22 LS Mean Change from Baseline for Trough FEV_1 (mL) over 24 Weeks (Studies 360 and 374)



Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

4.2.4.3. Secondary Endpoint: 0 to 6 hour Weighted Mean FEV_1 at Day 168 (Week 24)

In study 360, statistically significant increases in 0 to 6 hour weighted mean FEV_1 were demonstrated for comparisons of UMEC/VI 62.5/25 and 125/25 mcg with VI 25 mcg at Day 168 (Week 24) (Table 30 and Figure 23), demonstrating the contribution of UMEC to the combination. Additionally, both doses of UMEC/VI demonstrated statistically significant improvements in 0 to 6 hour weighted mean FEV_1 compared with tiotropium.

In study 374, comparisons of 0 to 6 hour weighted mean FEV_1 for UMEC/VI 62.5/25 and 125/25 mcg with UMEC 125 mcg and tiotropium achieved p-values of <0.05. However, p-values are nominal for these comparisons as a result of a prior test failure in the pre-defined study testing hierarchy as described in Section 4.2.4.1.

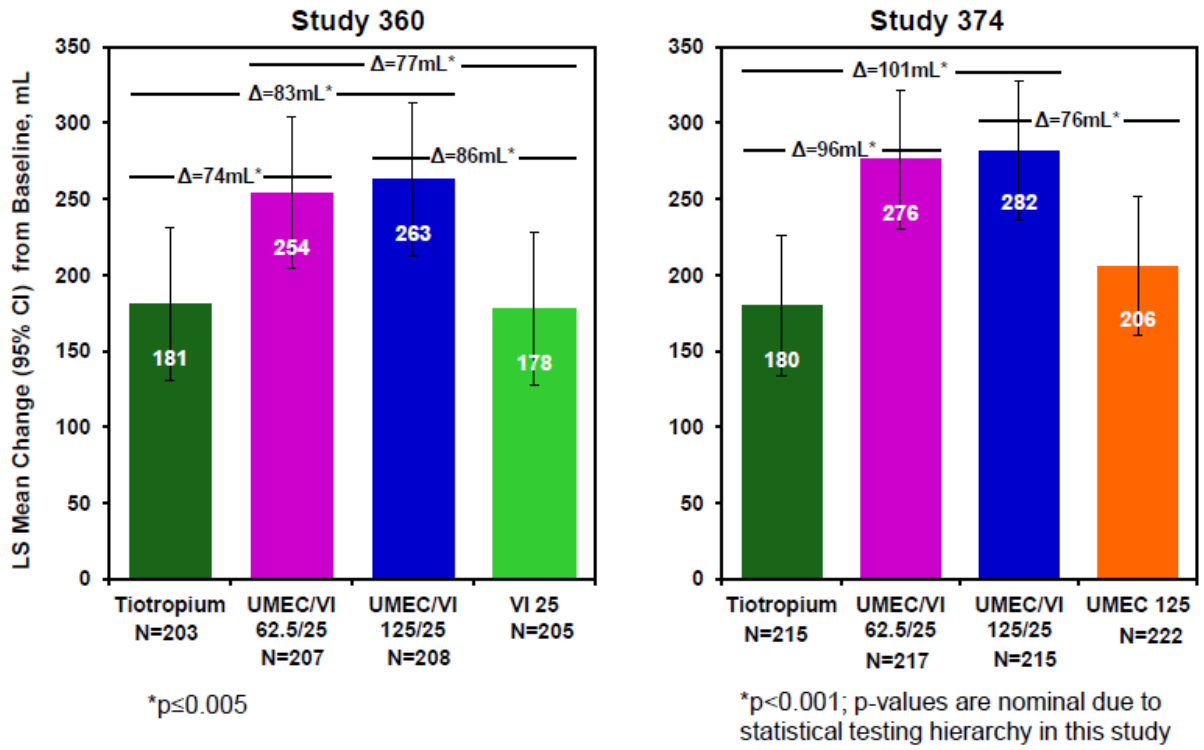
Table 30 Secondary Efficacy Analysis: 0 to 6 hour Weighted Mean FEV_1 (mL) at Day 168 (Studies 360 and 374)

DB2113360	VI 25 N=205	UMEC/VI 62.5/25 N=207	UMEC/VI 125/25 N=208	TIO N=203
LS mean (SE) LS mean change from baseline (SE)	1491 (18.9) 178 (18.9)	1567 (18.3) 254 (18.3)	1576 (18.7) 263 (18.7)	1494 (18.7) 181 (18.7)
UMEC/VI vs. VI 95% CI p-value		77 (25,128) 0.004	86 (33,138) 0.001	
UMEC/VI vs. tiotropium 95% CI p-value		74 (22,125) 0.005	83 (31,134) 0.002	
DB2113374	UMEC 125 N=222	UMEC/VI 62.5/25 N=217	UMEC/VI 125/25 N=215	TIO N=215
LS mean (SE) LS mean change from baseline (SE)	1351 (16.7) 206 (16.7)	1422 (16.8) 276 (16.8)	1427 (16.7) 282 (16.7)	1326 (16.5) 180 (16.5)
UMEC/VI vs. UMEC 125 95% CI p-value		70 (24, 117) 0.003 [a]	76 (29, 122) 0.001 [a]	
UMEC/VI vs. tiotropium 95% CI p-value		96 (50, 142) <0.001 [a]	101 (55, 147) <0.001 [a]	

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

a. p-values are nominal for this comparison according to the terms of the testing hierarchy for study 374.

Figure 23 LS Mean Change from Baseline for 0 to 6 hour Weighted Mean FEV_1 (mL) at Day 168 (Studies 360 and 374)

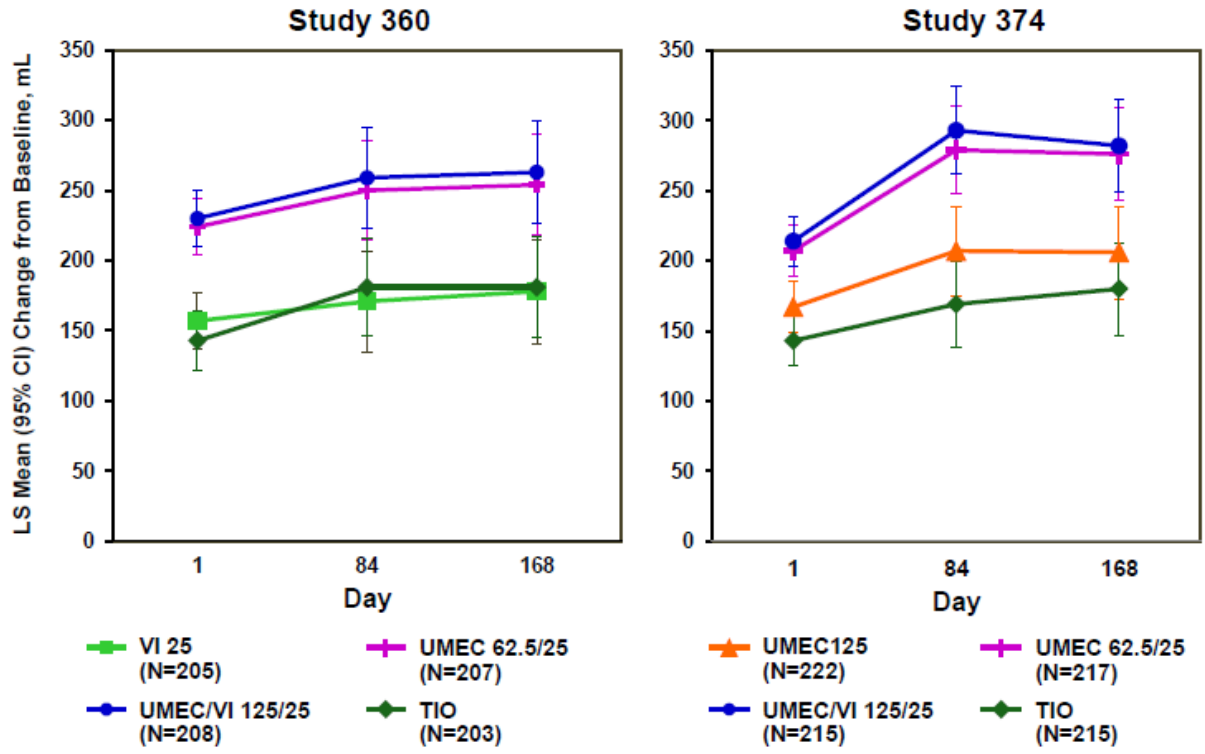


Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

4.2.4.4. 0 to 6 hour Weighted Mean FEV_1 over 24 Weeks

Both doses of UMEC/VI (62.5/25 and 125/25 mcg) showed statistically significant increases in 0 to 6 hour weighted mean FEV_1 at all assessments compared with tiotropium and VI 25 mcg in study 360 (Figure 24). Increases in 0 to 6 hour weighted mean FEV_1 compared with tiotropium and UMEC 125 mcg were demonstrated for both doses of UMEC/VI at all assessments in study 374.

Figure 24 **LS Mean Change from Baseline for 0 to 6 hour Weighted Mean FEV_1 (mL) over Time (Studies 360 and 374)**



Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

4.2.5. Patient-reported Measures and Health-related Quality of Life

Assessment of symptomatic benefit was based on subject-reported use of rescue albuterol, TDI focal score, and SOBDA score. Health-related quality of life was assessed by SGRQ score.

Consistent with the prescribing information for other long-acting bronchodilators, a description of the findings for rescue albuterol use and the SGRQ score from the placebo-controlled studies is intended to be included in the product prescribing information.

As these endpoints were supportive of the lung function findings, the primary comparison of interest for these measures was UMEC/VI with placebo. Therefore, the focus of the presentation of results is on the placebo-controlled studies and treatment differences for UMEC/VI and placebo. Results for the components from these studies are also provided.

4.2.5.1. Rescue Albuterol Use

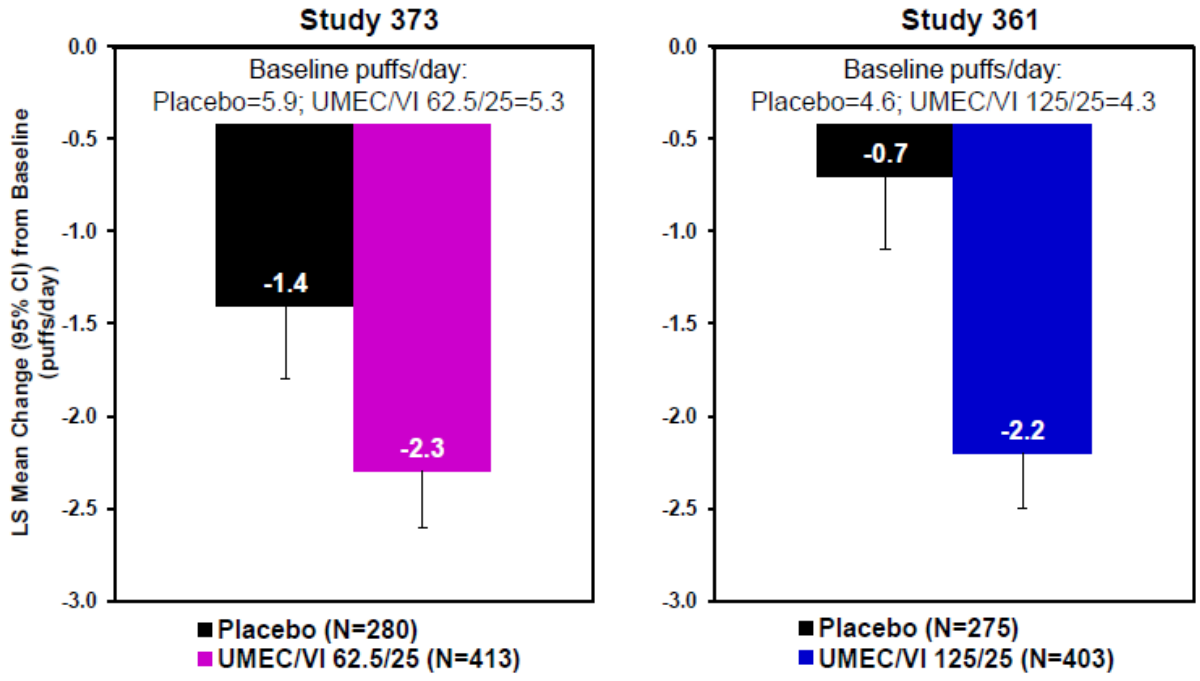
Over the 24-week treatment period, each dose of UMEC/VI (62.5/25 and 125/25 mcg) demonstrated a statistically significant reduction in rescue albuterol use compared with placebo (Table 31 and Figure 25).

Table 31 Analysis of Mean Number of Puffs of Rescue Medication Per Day over Weeks 1 to 24 (Studies 373 and 361)

Study 373	Placebo N=280	UMEC 62.5 N=418	VI 25 N=421	UMEC/VI 62.5/25 N=413
LS mean (SE) LS mean change from baseline (SE)	4.1 (0.20) -1.4 (0.20)	3.8 (0.16) -1.7 (0.16)	3.2 (0.16) -2.4 (0.16)	3.3 (0.16) -2.3 (0.16)
Difference vs. Placebo 95% CI p-value		-0.3 (-0.8, 0.2) 0.276	-0.9 (-1.4, -0.4) <0.001	-0.8 (-1.3, -0.3) 0.001
Study 361	Placebo N=275	UMEC 125 N=407	VI 25 N=404	UMEC/VI 125/25 N=403
LS mean (SE) LS mean change from baseline (SE)	3.7 (0.18) -0.7 (0.18)	2.8 (0.14) -1.5 (0.14)	2.9 (0.14) -1.5 (0.14)	2.2 (0.14) -2.2 (0.14)
Difference vs. Placebo 95% CI p-value		-0.8 (-1.3,-0.4) <0.001	-0.8 (-1.2,-0.3) <0.001	-1.5 (-1.9,-1.0) <0.001

Abbreviations: CI=confidence interval; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol

Figure 25 LS Mean Change from Baseline in Mean Number of Puffs of Rescue Medication per Day over Weeks 1-24 (Studies 373 and 361)



p≤0.001 for comparisons of UMEC/VI (62.5/25 and 125.25) with placebo

Abbreviations: LS=least squares; UMEC=umeclidinium bromide; VI=vilanterol

4.2.5.2. SGRQ

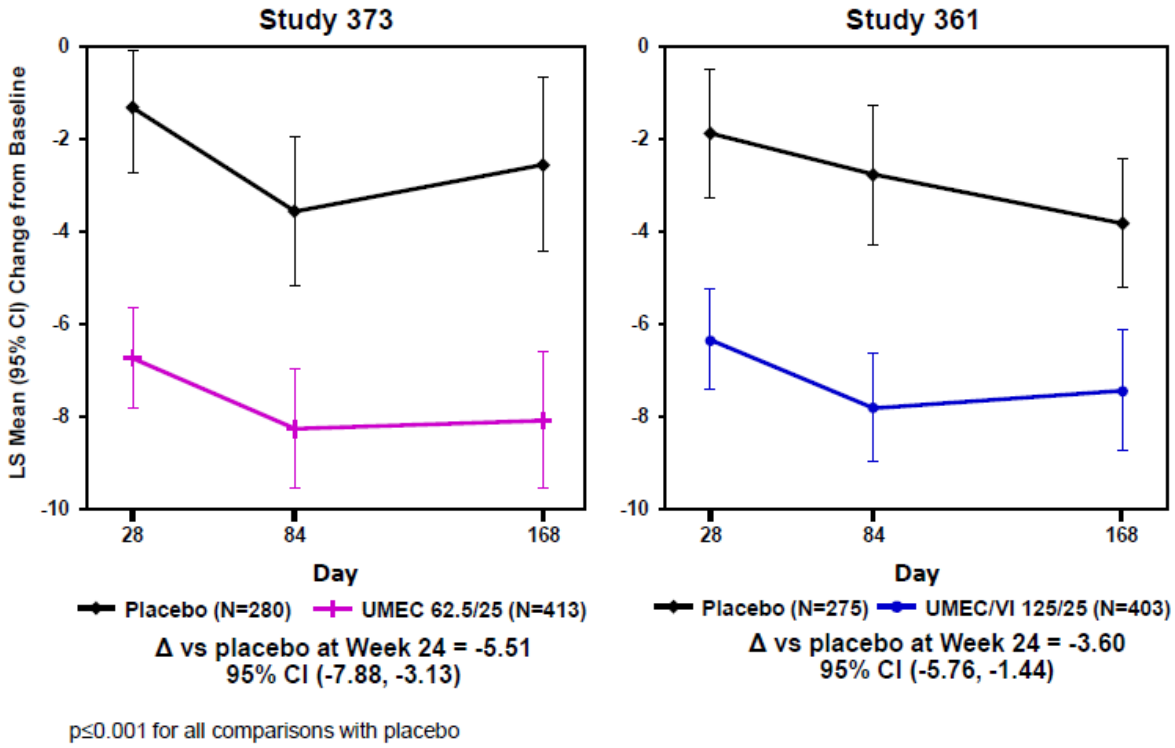
Both doses of UMEC/VI (62.5/25 and 125/25 mcg) demonstrated improvements in health-related quality of life compared with placebo as measured by the SGRQ total score (Table 32). Improvements (i.e., reductions in SGRQ score) at Day 168 (Week 24) were statistically significant and the mean difference was proximate to the MCID of -4.0 units for comparisons of UMEC/VI with placebo. Additionally, UMEC/VI 62.5/25 and 125/25 demonstrated consistent improvements over placebo in SGRQ total score throughout the study (Figure 26).

Table 32 Analysis of SGRQ Score at Day 168 (Studies 373 and 361)

Study 373	Placebo N=280	UMEC 62.5 N=418	VI 25 N=421	UMEC/VI 62.5/25 N=413
LS mean (SE) LS mean change from baseline (SE)	46.62 (0.950) -2.56 (0.950)	41.93 (0.753) -7.25 (0.753)	41.43 (0.760) -7.75 (0.760)	41.11 (0.749) -8.07 (0.749)
Difference vs. Placebo 95% CI p-value		-4.69 (-7.07,-2.31) <0.001	-5.19 (-7.58,-2.80) <0.001	-5.51 (-7.88,-3.13) <0.001
Study 361	Placebo N=275	UMEC 125 N=407	VI 25 N=404	UMEC/VI 125/25 N=403
LS mean (SE) LS mean change from baseline (SE)	43.69 (0.875) -3.83 (0.875)	43.38 (0.664) -4.14 (0.664)	42.82 (0.681) -4.71 (0.681)	40.10 (0.665) -7.43 (0.665)
Difference vs. Placebo 95% CI p-value		-0.31 (-2.46,1.85) 0.778	-0.87 (-3.05,1.30) 0.432	-3.60 (-5.76,-1.44) 0.001

Abbreviations: CI=confidence interval; LS=least squares; SE=standard error; SGRQ=St. George's Respiratory Questionnaire; UMEC=umeclidinium bromide; VI=vilanterol.

Figure 26 LS Mean Change from Baseline in SGRQ Total Score over Time (Studies 373 and 361)



Abbreviations: CI=confidence interval; LS=least squares; SGRQ=St. George's Respiratory Questionnaire; UMEC=umeclidinium bromide; VI=vilanterol
Note: Analysis included other treatment arms.

A responder analysis demonstrated that more subjects treated with UMEC/VI 62.5/25 or 125/25 mcg experienced an improvement from baseline in SGRQ score that met or exceeded the MCID of -4.0 units compared with subjects who received placebo (Table 33). This result was demonstrated for each dose of UMEC/VI in Study 373 and 361, respectively, and was highly consistent in the effect observed versus placebo.

Table 33 SGRQ Responder Analysis at Day 168 (Studies 373 and 361)

Study 373	Placebo N=280	UMEC 62.5 N=418	VI 25 N=421	UMEC/VI 62.5/25 N=413
Responder, n (%) [a] Non-responder, n (%)	86 (34) 168 (66)	172 (44) 216 (56)	181 (48) 200 (52)	188 (49) 193 (51)
Odds ratio vs. placebo 95% CI p-value		1.6 (1.2, 2.3) 0.003	1.9 (1.3, 2.6) <0.001	2.0 (1.4, 2.8) <0.001
Study 361	Placebo N=275	UMEC 125 N=407	VI 25 N=404	UMEC/VI 125/25 N=403
Responder, n (%) [a] Non-responder, n (%)	80 (37) 139 (63)	144 (40) 217 (60)	145 (41) 208 (59)	173 (49) 183 (51)
Odds ratio vs. placebo 95% CI p-value		1.2 (0.8, 1.7) 0.345	1.2 (0.9, 1.7) 0.254	1.7 (1.2, 2.4) 0.002

Abbreviations: CI=confidence interval; SGRQ=St. George's Respiratory Questionnaire; UMEC=umeclidinium bromide; VI=vilanterol

a. Response is defined as an SGRQ total score of 4 units below baseline (score prior to dosing on Day 1) or lower.

4.2.5.3. TDI Focal Score

Both doses of UMEC/VI (62.5/25 and 125/25 mcg) demonstrated improvements in dyspnea compared with placebo as measured by the TDI focal score (Table 34). Improvements in TDI focal score at Day 168 (Week 24) were statistically significant and the mean difference met or exceeded the MCID score of 1.0 unit for comparisons with placebo.

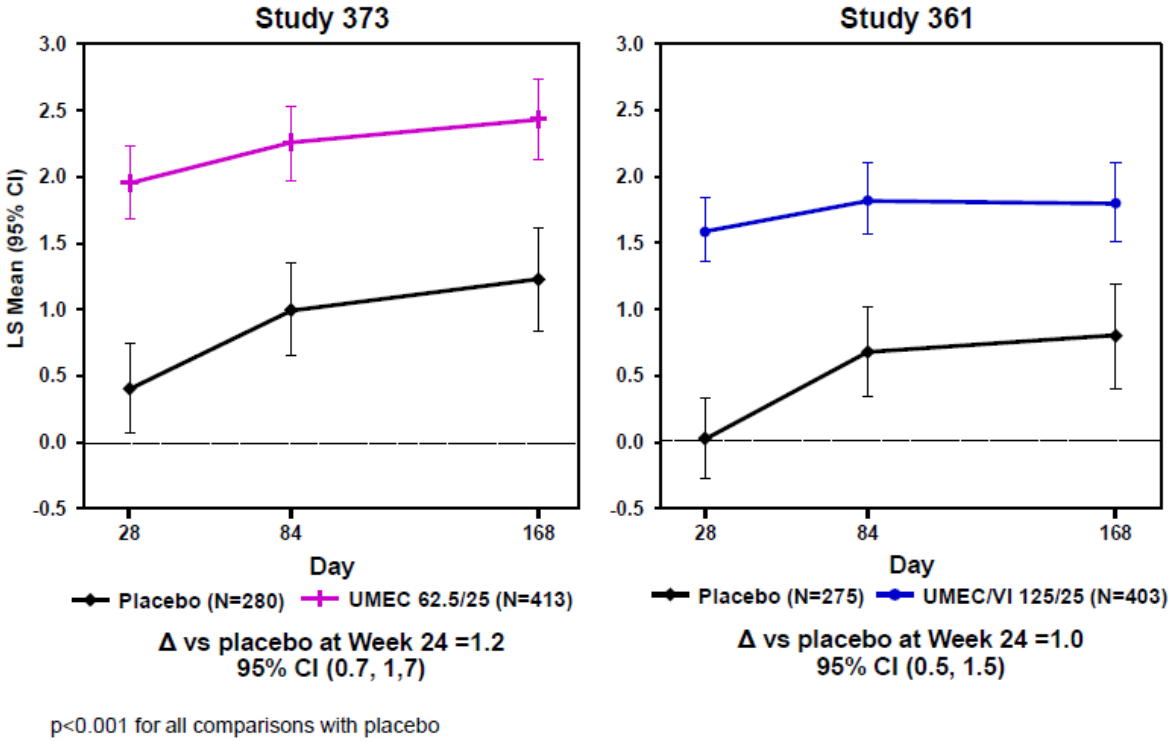
The improvements over placebo in TDI score with UMEC/VI treatment observed at the initial assessment at Day 28 were maintained throughout the study (Figure 27).

Table 34 Analysis of TDI Focal Score at Day 168 (Studies 373 and 361)

Study 373	Placebo N=280	UMEC 62.5 N=418	VI 25 N=421	UMEC/VI 62.5/25 N=413
LS mean (SE)	1.2 (0.20)	2.2 (0.16)	2.1 (0.16)	2.4 (0.16)
Difference vs. Placebo 95% CI p-value		1.0 (0.5,1.5) <0.001	0.9 (0.4,1.4) <0.001	1.2 (0.7,1.7) <0.001
Study 361	Placebo N=275	UMEC 125 N=407	VI 25 N=404	UMEC/VI 125/25 N=403
LS mean (SE)	0.8 (0.20)	1.2 (0.16)	1.3 (0.16)	1.8 (0.15)
Difference vs. Placebo 95% CI p-value		0.4 (-0.1,0.9) 0.108	0.5 (0.0,1.0) 0.054	1.0 (0.5,1.5) <0.001

Abbreviations: CI=confidence interval; LS=least squares; SE=standard error; TDI=transition dyspnea index; UMEC=umeclidinium bromide; VI=vilanterol

Figure 27 LS Mean TDI Focal Score over Time (Studies 373 and 361)



Abbreviations: CI=confidence interval; LS=least squares; TDI=transition dyspnea index; UMEC=umeclidinium bromide; VI=vilanterol
Note: Analysis included other treatment arms.

A responder analysis demonstrated that more subjects treated with UMEC/VI 62.5/25 and 125/25 mcg reported a TDI focal score that met or exceeded the MCID compared with subjects who received placebo (Table 35).

Table 35 Analysis of Proportion of Responders According to TDI Focal Score at Day 168 (Studies 373 and 361)

Study 373	Placebo N=280	UMEC 62.5 N=418	VI 25 N=421	UMEC/VI 62.5/25 N=413
Responder, n(%) [a] Non-responder, n(%)	106 (41) 154 (59)	207 (53) 187 (47)	197 (51) 192 (49)	226 (58) 163 (42)
Odds Ratio vs. Placebo 95% CI p-value		1.6 (1.2, 2.3) 0.002	1.5 (1.1, 2.1) 0.013	2.0 (1.5, 2.8) <0.001
Study 361	Placebo N=275	UMEC 125 N=407	VI 25 N=404	UMEC/VI 125/25 N=403
Responder, n(%) [a] Non-responder, n(%)	70 (30) 164 (70)	153 (41) 223 (59)	137 (38) 225 (62)	183 (49) 188 (51)
Odds Ratio vs. Placebo 95% CI p-value		1.7 (1.2, 2.4) 0.006	1.5 (1.0, 2.1) 0.037	2.5 (1.7, 3.5) <0.001

Abbreviations: CI=confidence interval; LS=least squares; SE=standard error; TDI=transition dyspnea index; UMEC=umeclidinium bromide; VI=vilanterol
Note: Response was defined as a TDI focal score of at least 1 unit.

4.2.5.4. SOBDA Score

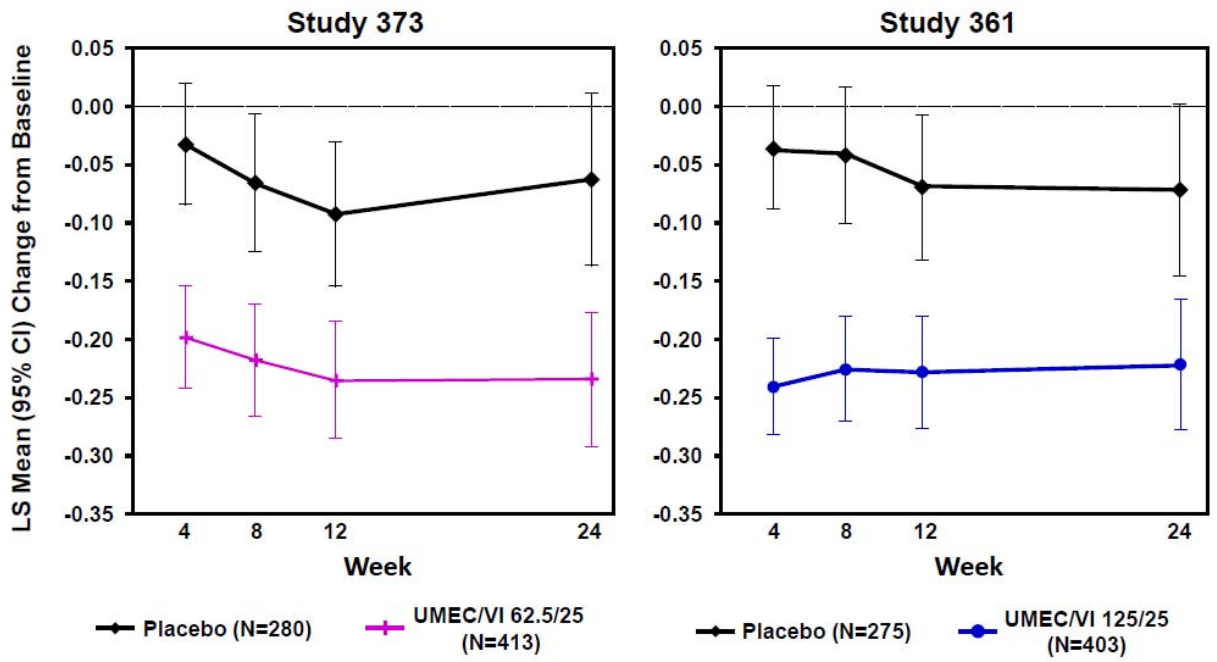
Both doses of UMEC/VI (62.5/25 and 125/25 mcg) demonstrated improvements in patient-reported dyspnea with daily activities compared with placebo as measured by the SOBDA questionnaire (Table 36). Reductions (i.e., improvements) in mean SOBDA score at Week 24 were statistically significant compared with placebo. Improvements in SOBDA score with both doses of UMEC/VI were maintained over the 24-week treatment periods (Figure 28).

Table 36 Analysis of SOBDA Score at Week 24 (Studies 373 and 361)

Study 373	Placebo N=280	UMEC 62.5 N=418	VI 25 N=421	UMEC/VI 62.5/25 N=413
LS mean (SE) LS mean change from baseline (SE)	1.94 (0.037) -0.06 (0.037)	1.84 (0.029) -0.16 (0.029)	1.79 (0.030) -0.21 (0.030)	1.77 (0.029) -0.23 (0.029)
Difference vs. Placebo 95% CI p-value		-0.10 (-0.19,0.00) 0.043	-0.14 (-0.24,-0.05) 0.002	-0.17 (-0.26,-0.08) <0.001
Study 361	Placebo N=275	UMEC 125 N=407	VI 25 N=404	UMEC/VI 125/25 N=403
LS mean (SE) LS mean change from baseline (SE)	1.89 (0.038) -0.07 (0.038)	1.81 (0.029) -0.15 (0.029)	1.86 (0.029) -0.10 (0.029)	1.74 (0.029) -0.22 (0.029)
Difference vs. Placebo 95% CI p-value		-0.08 (-0.17,0.02) 0.106	-0.03 (-0.13,0.06) 0.515	-0.15 (-0.24,-0.06) 0.002

Abbreviations: CI=confidence interval; LS=least squares; SE=standard error; SOBDA=Shortness of Breath with Daily Activities; UMEC=umeclidinium bromide; VI=vilanterol

Figure 28 LS Mean Change from Baseline in Mean SOBDA Score over Time (Studies 373 and 361)



Abbreviations: CI=confidence interval; LS=least squares; SOBDA=Shortness of Breath with Daily Activities; UMEC=umeclidinium bromide; VI=vilanterol
Note: Analysis included other treatment arms.

4.2.6. COPD Exacerbations

A COPD exacerbation was defined as an acute worsening of symptoms of COPD requiring the use of any treatment beyond study drug or rescue salbutamol.

The Primary Efficacy Studies were not specifically designed to evaluate the effect of treatments on COPD exacerbations and subjects were withdrawn if an exacerbation occurred. Additionally, subjects were not required to have a history of COPD exacerbations and protocol-specified symptom criteria were not used to define an exacerbation. Although these design aspects limit the interpretation of the exacerbation data, the results for time to first COPD exacerbation do indicate benefit from UMEC/VI 62.5/25 and 125/25 mcg compared with placebo. GSK does not, however, intend to include information describing the effect on the time to first COPD exacerbations in product prescribing information.

The overall incidence of on-treatment exacerbations was lower for UMEC/VI compared with placebo in both study 373 (7% and 13% for UMEC/VI 62.5/25 mcg and placebo, respectively) and study 361 (6% and 14% for UMEC/VI 125/25 mcg and placebo, respectively) (Table 37).

Analysis of time to first COPD exacerbation showed UMEC/VI 62.5/25 and 125/25 mcg resulted in a lower risk of COPD exacerbation compared with placebo (hazard ratios of 0.5 [95%CI: 0.3, 0.8] and 0.4 [95%CI: 0.2, 0.6], respectively, corresponding to risk reductions of 50% and 60%) (Table 37 and Figure 29).

Table 37 Summary and Analysis of Time to First COPD Exacerbation (Studies 373 and 361)

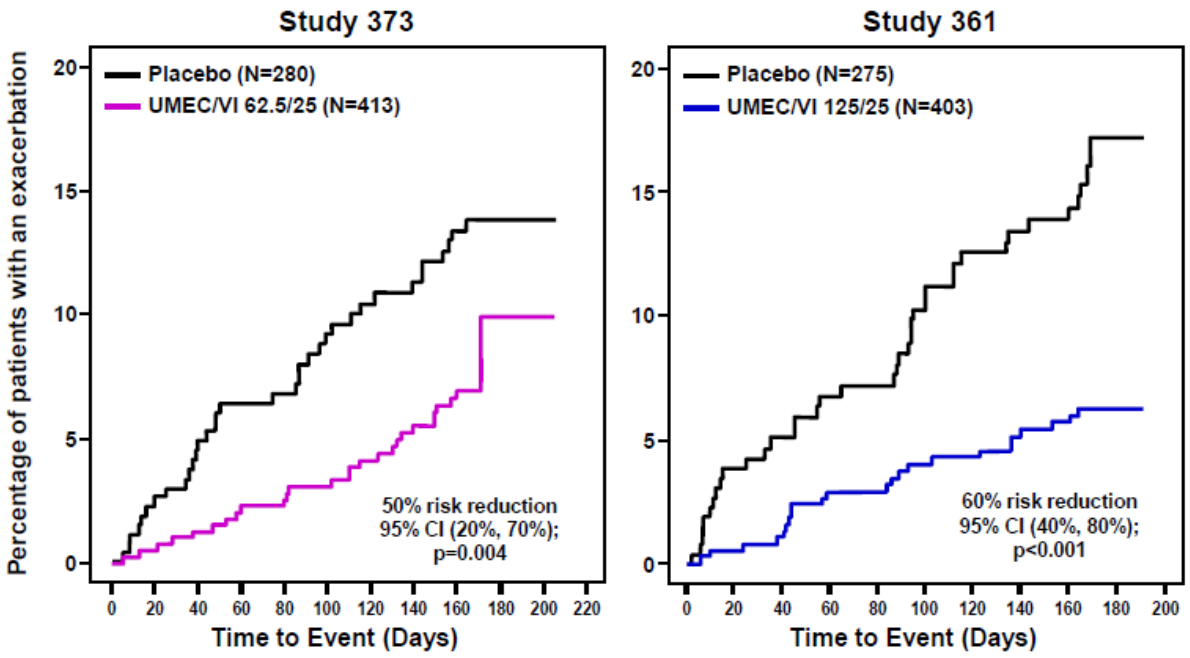
Study 373	Placebo N=280	UMEC 62.5 mcg N=418	VI 25 mcg N=421	UMEC/VI 62.5/25 mcg N=413
Number of subject with exacerbation Probability of having an exacerbation (%) 95% CI	35 (13) 13.7 (10.0, 18.6)	33 (8) 8.9 (6.4, 12.4)	39 (9) 11.7 (8.1, 16.8)	27 (7) 9.9 (5.2, 18.4)
Hazard Ratio vs. Placebo 95% CI p-value		0.6 (0.4, 1.0) 0.035	0.7 (0.4, 1.1) 0.137	0.5 (0.3, 0.8) 0.004
Study 361	Placebo N=275	UMEC 125 mcg N=407	VI 25 mcg N=404	UMEC/VI 125/25 mcg N=403
Number of subject with exacerbation Probability of having an exacerbation (%) 95% CI	38 (14) 17.1 (12.6, 23.1)	32 (8) 8.6 (6.1, 11.9)	32 (8) 9.2 (6.5, 12.8)	23 (6) 6.3 (4.2, 9.3)
Hazard Ratio vs. Placebo 95% CI p-value		0.5 (0.3, 0.8) 0.004	0.5 (0.3, 0.8) 0.006	0.4 (0.2, 0.6) <0.001

Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary disease; UMEC=umeclidinium bromide; VI=vilanterol

Note: Probability of having an event and 95% CI are taken from the Kaplan-Meier analysis.

Note: COPD exacerbation was defined as defined as an acute worsening of symptoms of COPD requiring the use of any treatment beyond study drug or rescue albuterol.

Figure 29 Time to First On-treatment COPD Exacerbation (days) (Studies 373 and 361)



Study 373: 7% of patients on UMEC/VI 62.5/25 mcg and 13% of patients on placebo experienced an exacerbation
Study 361: 6% of patients on UMEC/VI 125/25 mcg and 14% of patients on placebo experienced an exacerbation

Abbreviations: COPD=chronic obstructive pulmonary disease; UMEC=umeclidinium bromide; VI=vilanterol
Note: COPD exacerbation was defined as defined as an acute worsening of symptoms of COPD requiring the use of any treatment beyond study drug or rescue albuterol.
Note: Analysis included other treatment arms.

4.2.7. Missing Data Sensitivity Analyses for Primary Efficacy Studies

Missing data in the Primary Efficacy Studies was mainly due to subject withdrawal; the proportion of subjects excluded from analysis due to missing covariates was small (<2% in each study). A missing value between two non-missing values was implicitly interpolated in all analyses.

The extent of missing data due to early withdrawals in the Primary Efficacy Studies is shown by study in Table 38. In total, 33% or fewer patients withdrew from each treatment group in the individual Primary Efficacy Studies. Across treatment groups, the percentage of subjects withdrawing from the individual studies was higher in the placebo groups (33% and 27% in studies 361 and 373, respectively) than in the active treatment groups (range of 15 to 26%). The most common reason for early withdrawal was lack of efficacy. The reasons for withdrawal across treatment groups were consistent except for a larger proportion of subject withdrawals in the placebo group because of lack of efficacy (See Section 4.2.1, Table 24).

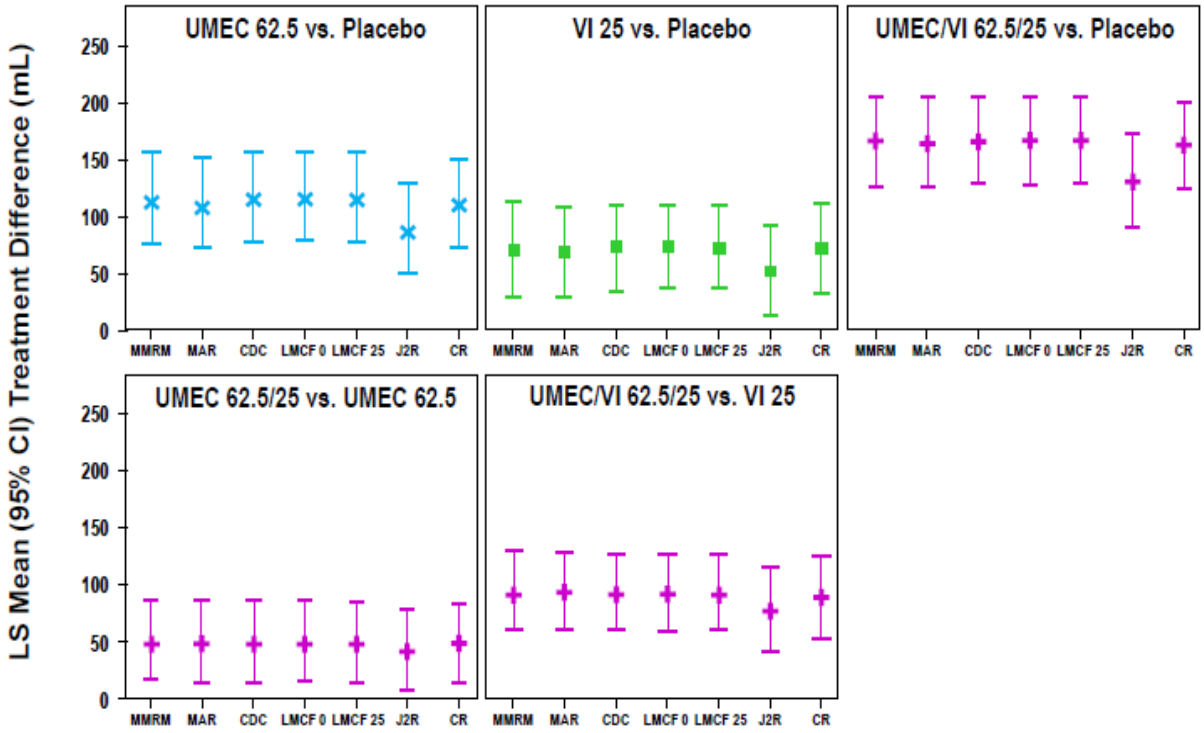
Table 38 Extent of Missing Data Due to Early Withdrawals for the Primary and Secondary Endpoint Analyses (Primary Efficacy Studies 361, 373, 360, and 374)

Study	Number of Subjects Withdrawn from the Study/ITT Population (%)							
	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO	Total
361	92/275 (33)		78/403 (19)		95/407 (23)	106/404 (26)		371/1489 (25)
373	76/280 (27)	81/413 (20)		94/418 (22)		103/421 (24)		354/1532 (23)
360		31/212 (15)	41/214 (19)			44/209 (21)	31/208 (15)	147/843 (17)
374		54/217 (25)	49/215 (23)		57/222 (26)		39/215 (18)	199/869 (23)

Abbreviations: ITT=intent-to-treat; TIO=tiotropium, UMEC=umeclidinium bromide; VI=vilanterol

As described in Section 3.3.6.5 and Appendix 10.3.2, sensitivity analyses using MI were conducted to assess the impact of missing data on efficacy conclusions. Results of the treatment comparisons for the primary and 6 sensitivity analyses conducted for trough FEV_1 in Study 373 are shown in Figure 30. In each case, the conclusions drawn from the sensitivity analyses were the same as those from the primary efficacy analysis. For example, in Study 373 the UMEC/VI difference from placebo in trough FEV_1 was 167 mL. For the more conservative sensitivity analysis (jump to reference [J2R]; where the reference treatment is placebo) the difference was, as expected, reduced, but was a statistically significant and clinically relevant difference of 132 mL. UMEC and VI differences from placebo, and UMEC/VI differences from components were also statistically significant in this more conservative sensitivity analysis.

Figure 30 LS Mean Treatment Differences in Change from Baseline for Trough FEV_1 at Day 169: Primary and Sensitivity Analyses (Study 373)



Abbreviations: CDC=copy differences from control multiple imputation method; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; J2R=jump to reference; LMCF 0=last mean carried forward (assuming decline of 0 mL/year; LMCF 25=last mean carried forward (assuming decline of 25 mL/year); LS=least squares; MMRM=mixed model repeated measures; MAR=missing at random multiple imputation methods; UMEC=umeclidinium bromide; VI=vilanterol
Note: Reference treatment is placebo.

Similar MI sensitivity analyses were conducted for the secondary endpoint of 0 to 6 hour weighted mean FEV_1, and other efficacy endpoints of SGRQ, SOBDA and TDI. In each case, the conclusions from analysis following MI were similar to those from the initial MMRM analysis.

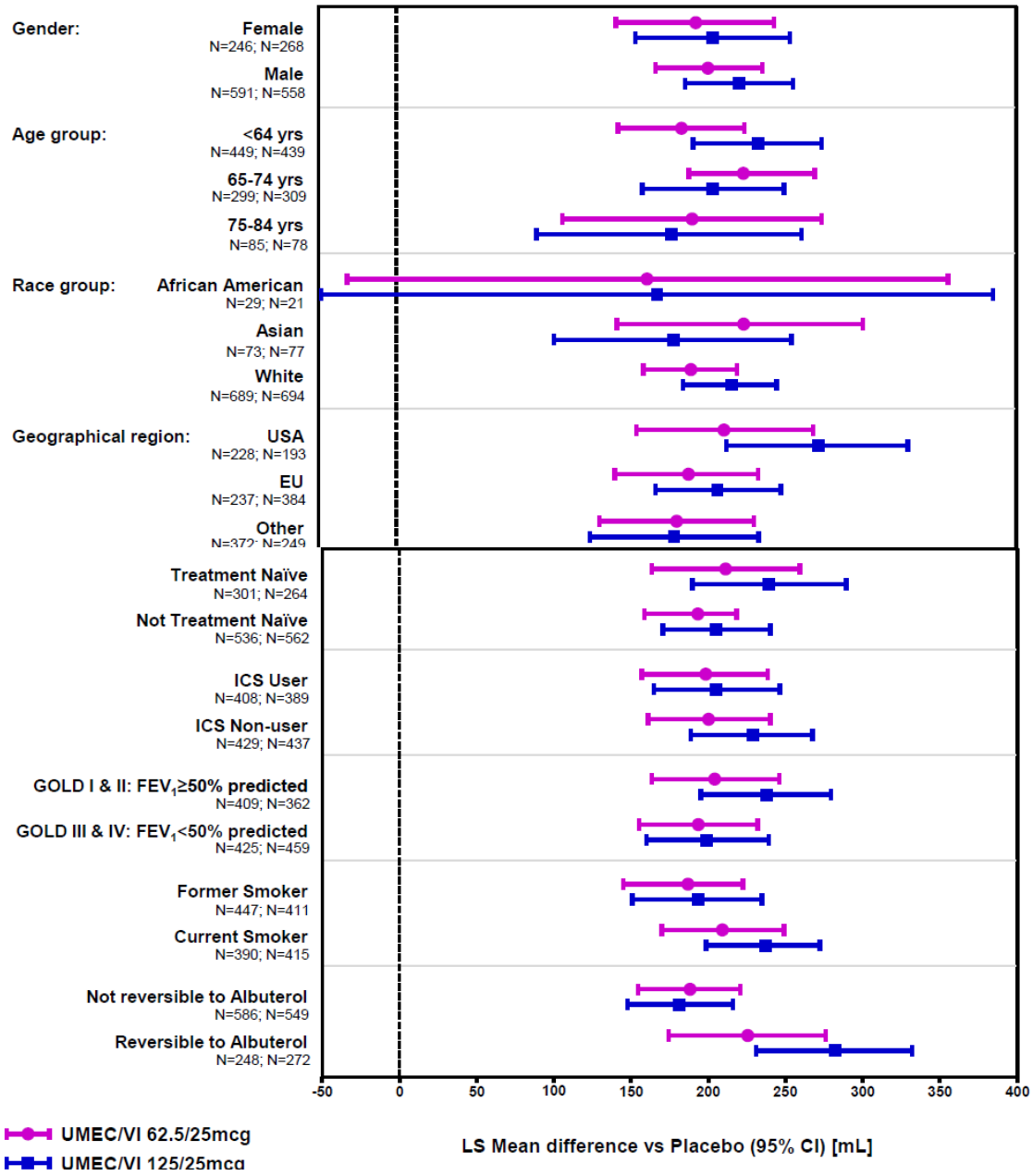
The results for MI sensitivity analyses for other studies are similarly consistent. The efficacy analyses are, therefore, considered robust to the impact of missing data.

4.2.8. Subgroup Analyses

There were no remarkable differences in efficacy in the various subgroups explored with the exception of reversibility to albuterol (Figure 31). For the reversibility to albuterol subgroup analyses of trough FEV_1, the response to treatment was in the same direction for both reversibility categories. However, the responses to active treatment were consistently greater in reversible subjects compared with non-reversible subjects. In addition, the reversible subjects showed a greater difference from placebo for UMEC/VI 125/25 mcg compared with that for

UMEC/VI 62.5/25 mcg. While these findings are of interest, further study is required to determine if there is a well-defined patient population(s) that would receive greater benefit from the UMEC/VI 125/25 mcg dose.

Figure 31 Forest Plots for Overall Subgroup Analyses: Trough FEV_1 at Day 169 (Integrated Primary Efficacy Studies 361, 373, 360, and 374)



Abbreviations: CI=confidence interval; EU=European Union; FEV_1=forced expiratory volume in 1 second; LS=least squares; LS=least squares; UMEC=umeclidinium bromide; US=United States; VI=vilanterol

Note: Because of the particularly small numbers of subjects in the ≥85 years age group and the Native Hawaiian or other Pacific Islander race subgroups, data for these subjects are not included in forest plots.

4.3. Long-term Safety Study 359

4.3.1. Subject Disposition

The majority of subjects (61%) completed study 359 (Table 39).

Table 39 Overall Subject Disposition (Study 359)

	Number (%) of Subjects			
	Placebo N=109	UMEC 125 N=227	UMEC/VI 125/25 N=226	Total N=562
Completion Status				
Completed [a]	66 (61)	133 (59)	143 (63)	342 (61)
Withdrawn	43 (39)	94 (41)	83 (37)	220 (39)
Primary reason/subreason for withdrawal [b]				
Adverse event	13 (12)	21 (9)	17 (8)	51 (9)
Lack of efficacy	9 (8)	3 (1)	1 (<1)	13 (2)
COPD exacerbations	4 (4)	1 (<1)	1 (<1)	6 (1)
Protocol deviations	2 (2)	6 (3)	6 (3)	14 (2)
Subject reached protocol-defined stopping criteria	8 (7)	37 (16)	36 (16)	81 (14)
ECG abnormality	0	12 (5)	13 (6)	25 (4)
Holter abnormality	8 (7)	26 (11)	26 (12)	60 (11)
Lab abnormality	0	1 (<1)	0	1 (<1)
Study closed/terminated	2 (2)	4 (2)	3 (1)	9 (2)
Lost to follow-up	1 (<1)	7 (3)	5 (2)	13 (2)
Withdrew consent	8 (7)	16 (7)	15 (7)	39 (7)
Subject relocated	1 (<1)	3 (1)	3 (1)	7 (1)
Frequency of visits	1 (<1)	2 (<1)	0	3 (<1)
Burden of procedures	0	3 (1)	3 (1)	6 (1)
Other	6 (6)	9 (4)	9 (4)	24 (4)

Abbreviations: COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; UMEC=umeclidinium bromide; VI=vilanterol

a. Subjects were considered to have completed if they completed the last clinic visit excluding follow-up (Visit 7) and did not withdraw at the visit.

b. Subjects only recorded 1 primary reason for withdrawal. Subjects were not required to indicate a subreason for all primary reasons, however, if they did, they could have marked more than 1, if appropriate.

4.3.2. Demographic and Baseline Characteristics

Demographic characteristics for study 359 were similar across treatment groups and comparable to the Primary Efficacy Studies (Table 40).

Table 40 Summary of Demographic Characteristics (Study 359)

Demographic Characteristic	Placebo N=109	UMEC 125 N=227	UMEC/VI 125/25 N=226	Total N=562
Age (years)				
Mean	60.1	61.7	61.4	61.3
SD	8.28	9.10	9.01	8.92
Min, Max	41, 82	40, 85	40, 84	40, 85
Gender				
Female, n (%)	36 (33)	82 (36)	70 (31)	188 (33)
Male, n (%)	73 (67)	145 (64)	156 (69)	374 (67)
Race				
White, n (%)	104 (95)	214 (94)	211 (93)	529 (94)
African American, n (%)	3 (3)	13 (6)	14 (6)	30 (5)
Asian, n (%)	2 (2)	0	1 (<1)	3 (<1)
Other, n (%)	0	0	0	0
Body Mass Index (kg/m^2), n				
Mean	27.65	28.05	27.89	27.91
SD	5.885	5.881	5.859	5.864
Min, Max	13.6, 43.3	17.3, 54.6	16.4, 51.3	13.6, 54.6

Abbreviations: Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol

Summary findings for baseline COPD and lung function characteristics are presented for study 359 in Table 41. More than half (63%) of the subjects were current smokers and approximately one third (34%) were using concurrent ICS therapy. The mean post-albuterol percent predicted FEV_1 was 54.7%. The majority of subjects (68%) did not report a COPD exacerbation requiring oral corticosteroids or antibiotics in the year prior to screening.

Table 41 Summary of Baseline COPD and Lung Function Characteristics (Study 359)

Parameter	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227	Total N=562
Years smoked, n	109	226	227	562
Mean (SD)	36.2 (9.18)	38.1 (11.38)	36.6 (11.49)	37.1 (11.05)
Min, Max	10, 54	10, 67	10, 70	10, 70
Smoking pack-years,n	109	226	227	562
Mean (SD)	42.8 (24.71)	43.7 (27.49)	39.2 (21.24)	41.7 (24.63)
Min, Max	10, 150	10, 236	8, 144	8, 236
Smoking status at Screening, n	109	226	227	562
Current smoker, n (%)	71 (65)	135 (60)	148 (65)	354 (63)
Former smoker, n (%)	38 (35)	91 (40)	79 (35)	208 (37)
Post-albuterol FEV_1 (L), n	109	224	225	558
Mean	1.724	1.647	1.594	1.641
SD	0.5691	0.5138	0.4884	0.5164
Post-albuterol FEV_1/FVC (%), n	109	224	225	558
Mean	53.197	52.187	51.681	52.180
SD	10.1012	9.9999	10.5522	10.2422
Post-albuterol Percent Predicted FEV_1 (%), n	109	224	225	558
Mean	55.1	55.0	54.2	54.7
SD	11.68	12.10	11.81	11.89
Reversibility to Albuterol [a], n	108	223	224	555
Not Reversible, n (%)	72 (67)	145 (65)	152 (68)	369 (66)
Reversibile, n (%)	36 (33)	78 (35)	72 (32)	186 (34)
ICS use at Screening, n	109	226	227	562
ICS user, n (%)	40 (37)	80 (35)	73 (32)	193 (34)
ICS non-user, n (%)	69 (63)	146 (65)	154 (68)	369 (66)
GOLD stage, n	109	224	225	558
I: $FEV_1 \geq 80\%$ predicted	1 (<1)	0	0	1 (<1)
II: $50\% \leq FEV_1 < 80\%$ predicted	71 (65)	137 (61)	129 (57)	337 (60)
III: $30\% \leq FEV_1 < 50\%$ predicted	37 (34)	87 (39)	96 (43)	220 (39)
IV: $FEV_1 < 30\%$ predicted	0	0	0	0
COPD type, n	109	225	227	561
Chronic bronchitis, n (%)	74 (68)	159 (71)	162 (71)	395 (70)
Emphysema, n (%)	71 (65)	154 (68)	149 (66)	374 (67)
COPD Exacerbations in Previous Year, n	109	226	226	561
Requiring oral steroids or antibiotics, n (%)				
0	70 (64)	155 (69)	155 (69)	380 (68)
≥1	39 (36)	71 (31)	71 (31)	181 (32)
Requiring hospitalization, n (%)				
0	91 (83)	190 (84)	195 (86)	476 (85)
≥1	18 (17)	36 (16)	31 (14)	85 (15)

Abbreviations: COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; GOLD=Global Initiative for Obstructive Lung Disease; ICS=inhaled corticosteroid; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol

a. Defined as an improvement in FEV_1 following administration of a short-acting bronchodilator of ≥12% and ≥200 mL from pre-treatment levels

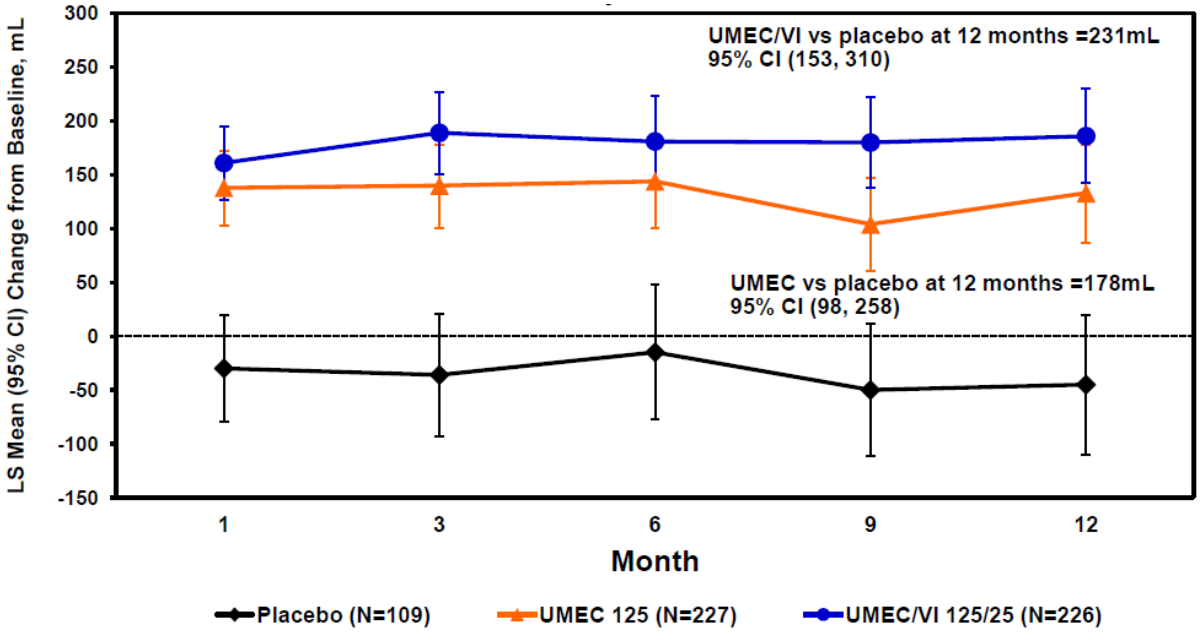
4.3.3. Trough FEV_1

As stated in Section 3.4.5.2, the study 359 sample size was based on providing an acceptable number of patients treated with UMEC/VI and UMEC for long-term evaluations of safety. As

such, the protocol specified that formal statistical hypothesis testing would not be performed. Trough FEV_1 data are provided as evidence of persistence of efficacy of UMEC/VI and UMEC over 12 months.

The UMEC/VI 125/25 mcg and UMEC 125 mcg treatment groups both demonstrated greater increases from baseline in trough FEV_1 compared with placebo at Month 12 (Figure 32). Improvements in trough FEV_1 were observed at Month 1 and maintained through Month 12.

Figure 32 LS Mean Change from Baseline for trough FEV_1 (mL) over 12 Months (Study 359)



Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; UMEC=umeclidinium bromide; VI=vilanterol

4.4. Exercise/Lung Function Studies 417 and 418

4.4.1. Subject Disposition

Overall, 73% of subjects completed the Exercise/Lung Function Studies (Table 42).

Table 42 Overall Subject Disposition (Integrated Exercise/Lung Function Studies 417 and 418)

	Number (%) of Subjects						
	Placebo N=321	UMEC/VI 62.5/25 N=282	UMEC/VI 125/25 N=272	UMEC 62.5 N=89	UMEC 125 N=91	VI 25 N=140	Total N=655
Completion Status							
Completed [a]	267 (83)	242 (86)	236 (87)	80 (90)	76 (84)	114 (81)	475 (73)
Withdrawn	54 (17)	40 (14)	36 (13)	9 (10)	15 (16)	26 (19)	180 (27)
Primary Reason/Subreason for Withdrawal [b]							
Adverse event	16 (5)	12 (4)	10 (4)	3 (3)	3 (3)	9 (6)	53 (8)
Lack of efficacy	26 (8)	13 (5)	15 (6)	2 (2)	7 (8)	9 (6)	72 (11)
Exacerbation	20 (6)	12 (4)	13 (5)	2 (2)	7 (8)	8 (6)	62 (9)
Protocol deviation	3 (<1)	2 (<1)	3 (1)	0	1 (1)	2 (1)	11 (2)
Subject reached protocol-defined stopping criteria	0	4 (1)	0	1 (1)	0	1 (<1)	6 (<1)
ECG abnormality	0	4 (1)	0	1 (1)	0	1 (<1)	6 (<1)
Lab abnormality	0	0	0	0	0	0	0
Study closed/terminated	0	0	1 (<1)	0	0	0	1 (<1)
Lost to follow-up	3 (<1)	2 (<1)	4 (1)	0	1 (1)	2 (1)	12 (2)
Withdrew consent	6 (2)	7 (2)	3 (1)	3 (3)	3 (3)	3 (2)	25 (4)
Subject relocated	2 (<1)	2 (<1)	0	0	0	0	4 (<1)
Frequency of visits	0	0	1 (<1)	1 (1)	0	0	2 (<1)
Burden of procedures	2 (<1)	1 (<1)	0	0	1 (1)	2 (1)	6 (<1)
Other	2 (<1)	4 (1)	2 (<1)	2 (2)	3 (3)	1 (<1)	14 (2)

Abbreviations: ECG=electrocardiogram; UMEC=umeclidinium bromide; VI=vilanterol

Note: Subjects who completed both treatment periods are counted as a completer under each treatment received and the total column. Subjects who withdrew prior to Period 2 are counted as a withdrawal in both their Period 1 treatment and the total column. Subjects who withdrew during Period 2 are counted as a completer under their Period 1 treatment and as a withdrawal under their Period 2 treatment and the total column.

a. Subjects were considered to have completed the Treatment Period if they attended the last clinic visit and did not withdraw at that visit.

b. Subjects only recorded 1 primary reason for withdrawal and were not required to indicate sub-reasons. However, subjects could have selected more than 1 sub-reason if appropriate.

4.4.2. Demographic and Baseline Characteristics

Demographic characteristics of subjects in the Exercise/Lung Function Studies were similar to those reported for the Primary Efficacy Studies (Table 43).

Table 43 Summary of Demographic Characteristics (Integrated Exercise/Lung Function Studies 417 and 418)

Demographic Characteristic	Placebo N=321	UMEC/VI 62.5/25 N=282	UMEC/VI 125/25 N=272	UMEC 62.5 N=89	UMEC 125 N=91	VI 25 N=140	Total N=655
Age (years), n	321	282	272	89	91	140	655
Mean	62.0	62.0	61.8	61.7	63.2	61.5	62.0
SD	8.20	7.88	8.25	7.92	8.77	8.21	8.09
Min, Max	42, 84	43, 81	41, 81	44, 84	44, 84	41, 81	41, 84
Sex, n	321	282	272	89	91	140	655
Female, n (%)	141 (44)	122 (43)	131 (48)	36 (40)	43 (47)	60 (43)	292 (45)
Male, n (%)	180 (56)	160 (57)	141 (52)	53 (60)	48 (53)	80 (57)	363 (55)
Race, n	321	282	272	89	91	140	655
White, n (%)	312 (97)	269 (95)	267 (98)	83 (93)	89 (98)	134 (96)	634 (97)
African American, n (%)	9 (3)	10 (4)	4 (1)	5 (6)	1 (1)	5 (4)	17 (3)
Asian, n (%)	0	1 (<1)	0	1 (1)	0	0	1 (<1)
Other, n (%)	0	2 (<1)	1 (<1)	0	1 (1)	1 (<1)	3 (<1)
Body Mass Index (kg/m^2), n	321	282	272	89	91	140	655
Mean	26.82	26.75	27.31	26.92	26.90	27.44	27.07
SD	5.457	5.224	5.792	6.439	5.961	5.431	5.736
Min, Max	15.1, 43.0	16.0, 47.5	15.1, 47.0	16.6, 62.8	15.2, 43.0	15.8, 47.0	15.1, 62.8

Abbreviations: Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
Note: Subjects are counted once under each treatment received and once in the Total column.

The mean post-albuterol percent predicted FEV_1 was 51.3%. Inhaled corticosteroid use was reported by 33% of subjects. Subjects were required to have documented hyperinflation to be eligible for participation. The mean percent predicted normal FRC was 153.6% in study 417 and 151.6% in study 418.

4.4.3. Co-Primary Endpoint: Exercise Endurance Time at Day 85 (Week 12)

In study 418, statistically significant and clinically meaningful (MCID between 45 and 85 seconds [Pepin, 2011]) increases in 3-hour postdose EET were demonstrated for both UMEC/VI doses compared with placebo at Week 12 (UMEC/VI 62.5/25 mcg: 69.4 sec [CI: 24.5, 114.4; p<0.003] and UMEC/VI 125/25 mcg: 65.8 sec [CI: 20.3, 111.3; p=0.005]).

In study 417, neither dose of UMEC/VI resulted in a statistically or clinically significant improvement in 3-hour postdose EET at Week 12 compared with placebo (UMEC/VI 62.5/25 mcg: 21.9 sec [CI: -14.2, 58.0; p=0.234] and UMEC/VI 125/25 mcg: 32.4 sec [CI: -3.9, 68.8; p=0.080]).

4.4.4. Co-Primary Endpoint: Trough FEV_1 at Day 85 (Week 12)

In study 418, both doses of UMEC/VI (62.5/25 and 125/25 mcg) demonstrated statistically significant increases in trough FEV_1 at Week 12 compared with placebo (Table 44). In study 417, numerical increases in trough FEV_1 at Week 12 were demonstrated for both doses of UMEC/VI compared with placebo (p<0.001); p-values are nominal for these comparisons however, as a prior test in the predefined testing hierarchy (i.e., 3-hour postdose EET at Week 12

for UMEC/VI 125/25 mcg vs. placebo [the first comparison in the testing hierarchy]) did not achieve statistical significance.

These Exercise/Lung Function Studies provide supportive evidence of efficacy for both doses of UMEC/VI (62.5/25 and 125/25 mcg), UMEC (62.5 and 125 mcg) and VI 25 mcg compared with placebo at Week 12, and for the contribution of each component to the efficacy of UMEC/VI 62.5/25 mcg. The response compared with placebo was consistent across the 2 studies for the UMEC/VI 62.5/25 mcg dose. There was no evidence of greater improvements in trough FEV_1 for the higher than with the lower UMEC/VI dose.

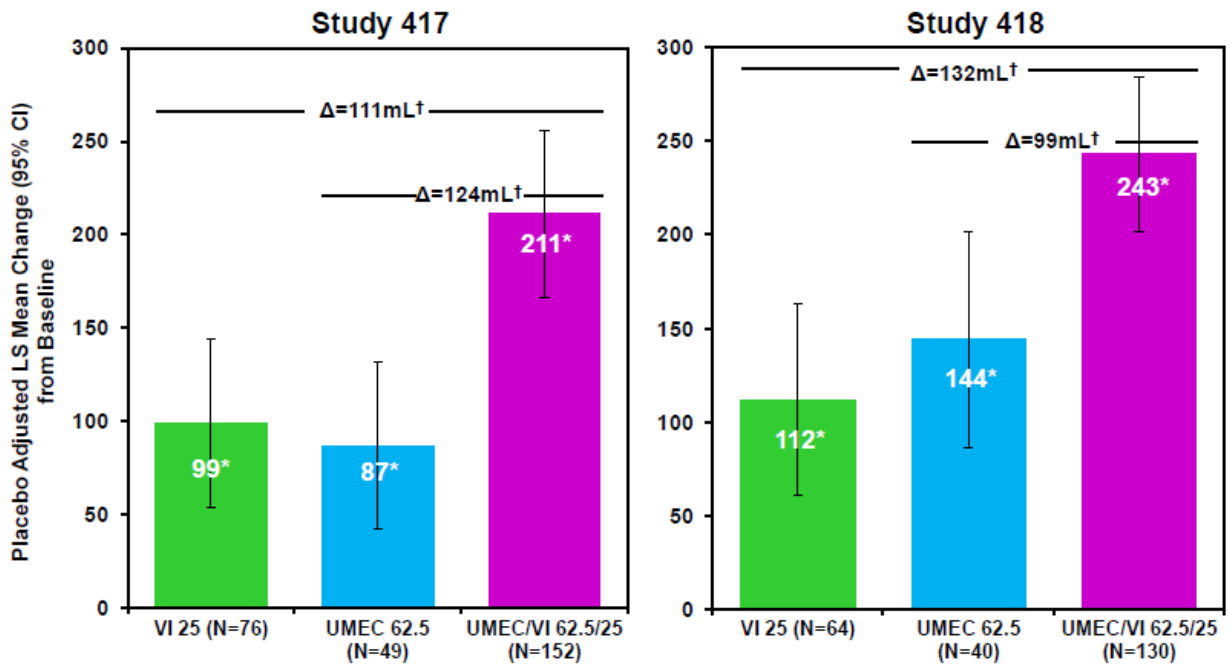
Table 44 Co-Primary Efficacy Analysis: Trough FEV_1 (mL) at Week 12 (Studies 417 and 418)

Week 12	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25
417, N	170	152	144	49	50	76
LS Mean Change from baseline (SE)	-32 (14.9)	178 (15.6)	136 (15.8)	54 (26.4)	108 (26.3)	67 (21.8)
Difference vs. Placebo 95% CI p-value		211 (172, 249) <0.001 [a]	169 (129, 209) <0.001 [a]	87 (30,143) 0.003 [a]	140 (84, 196) <0.001 [a]	99 (50, 148) <0.001 [a]
Difference vs. UMEC/VI 62.5/25 95% CI p-value				124 (67, 181) <0.001 [a]		111 (62, 161) <0.001 [a]
Difference vs. UMEC/VI 125/25 95% CI p-value					29 (-28, 86) 0.320 [a]	70 (19, 120) 0.007 [a]
418, N	151	130	128	40	41	64
LS Mean Change from baseline (SE)	-43 (15.6)	200 (15.6)	218 (15.9)	101 (26.7)	212 (28.7)	69 (22.2)
Difference vs. Placebo 95% CI p-value		243 (202, 284) <0.001	261 (220,303) <0.001	144 (86, 203) <0.001	255 (193, 318) <0.001	112 (61, 163) <0.001
Difference vs. UMEC/VI 62.5/25 95% CI p-value				99 (41, 157) <0.001		132 (81, 183) <0.001
Difference vs. UMEC/VI 125/25 95% CI p-value					6 (-55, 67) 0.849	150 (98, 201) <0.001

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol

a. p-values are nominal for this comparison according to the terms of the testing hierarchy for study 417.

Figure 33 Placebo-Adjusted LS Mean Change from Baseline for Trough FEV_1 (mL) at Week 12 (Studies 417 and 418)



*p≤0.003 for comparisons of UMEC/VI 62.5/25, UMEC 62.5, and VI with placebo
†p<0.001 for comparisons of UMEC/VI 62.5/25 with UMEC 62.5 and VI

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; UMEC=umeclidinium bromide; VI=vilanterol
Note: p-values are nominal for comparisons in study 417 as a result of a prior test failure in the predefined testing hierarchy.

4.5. Summary of Trough FEV_1 Data Demonstrating the Efficacy of UMEC 62.5 mcg and VI 25 mcg Monotherapy

Neither of the components of UMEC/VI 62.5/25 is approved as a monotherapy for the treatment of COPD. Therefore, an important aspect of the clinical development program was to demonstrate the efficacy of the UMEC and VI components as compared with placebo.

Data supporting the efficacy of the UMEC 62.5 mcg and VI 25 mcg components were obtained from the 24-week Primary Efficacy Studies (primary endpoint of trough FEV_1) and the 12-week Exercise/Lung Function Studies (co-primary endpoint of trough FEV_1) (Table 45). In all these studies, the efficacy of UMEC 62.5 mcg and VI 25 mcg was confirmed by improvements in trough FEV_1 compared with placebo. These data demonstrate that the doses of UMEC and VI selected for the combination product are efficacious.

Table 45 Summary of Efficacy of UMEC 62.5 mcg and VI 25 mcg for Trough FEV_1

	Time Point	Treatment Difference (mL)	95% CI	p-value
UMEC 62.5 vs. placebo				
Study 373	Day 169	115	76, 155	<0.001
Study 417	Week 12	87	30, 143	0.003 [a]
Study 418	Week 12	144	86, 203	<0.001
VI 25 vs. placebo				
Study 361	Day 169	124	86, 162	<0.001
Study 373	Day 169	72	32, 112	<0.001
Study 417	Week 12	99	50, 148	<0.001 [a]
Study 418	Week 12	112	61, 163	<0.001

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; UMEC=umeclidinium bromide; VI=vilanterol
Note: The individual Primary Efficacy Studies were powered for the comparisons presented in this table. The individual Exercise/Lung Function Studies were not powered for the comparisons presented in this table and are considered supportive of the powered comparisons.
a. p-values are nominal for this comparison according to the terms of the testing hierarchy for study 417.

4.6. Summary of Trough FEV_1 Data Demonstrating the Contribution of UMEC 62.5 mcg and VI 25 mcg to the Efficacy of UMEC/VI 62.5/25

Data demonstrating that both UMEC 62.5 mcg and VI 25 mcg contribute to the efficacy of UMEC/VI 62.5/25 mcg were obtained from the 24-week Primary Efficacy Studies (primary endpoint of trough FEV_1) and the 12-week Exercise/Lung Function Studies (co-primary endpoint of trough FEV_1). Across these studies:

- All comparisons (across 4 studies) of UMEC 62.5/25 mcg with VI 25 mcg demonstrated improvements in trough FEV_1, confirming the contribution of UMEC 62.5 mcg to the efficacy of the combination.
- All comparisons (across 3 studies) of UMEC 62.5/25 mcg with UMEC 62.5 mcg demonstrated improvements in trough FEV_1, confirming the contribution of VI 25 mcg to the efficacy of the combination.

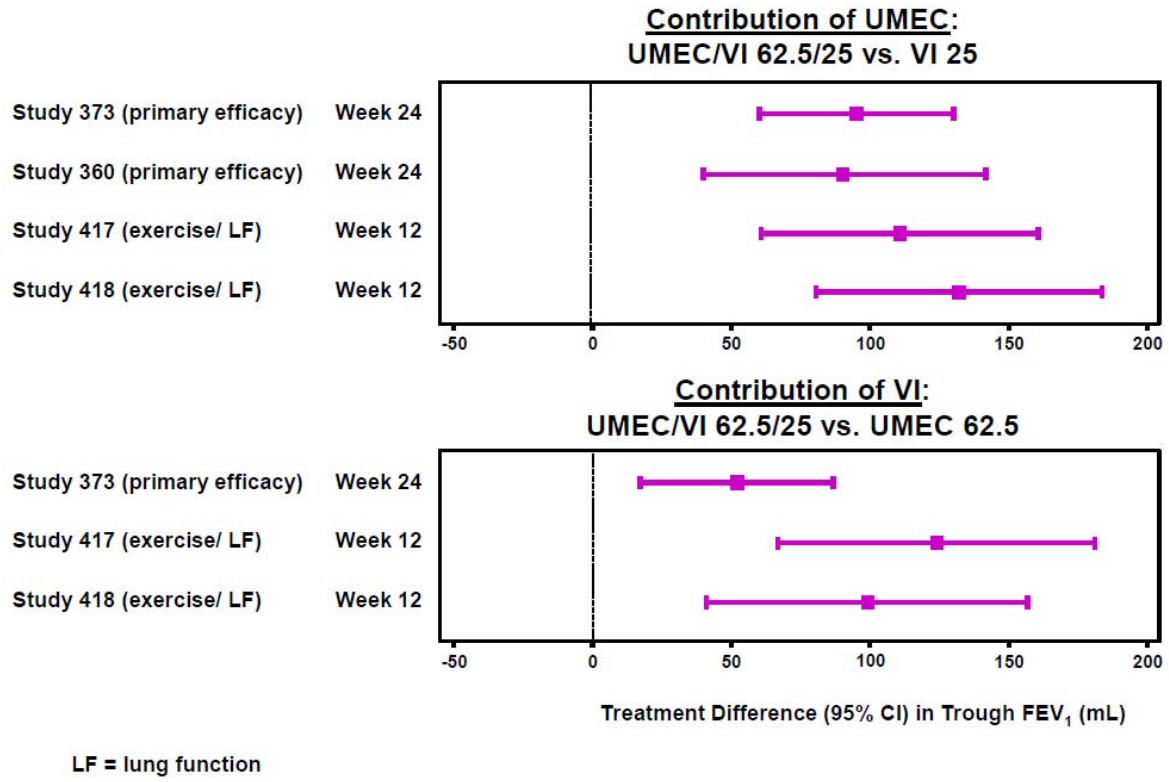
A summary of trough FEV_1 results for comparisons of UMEC/VI 62.5/25 mcg with the components is provided in Table 46 and displayed in Figure 34.

Table 46 Summary of Data Demonstrating the Contribution of UMEC 62.5 and VI 25 mcg to the Efficacy of UMEC/VI 62.5/25 mcg for Trough FEV_1

	Time Point	Treatment Difference (mL)	95% CI	p-value
Contribution of UMEC 62.5: Comparison of UMEC/VI 62.5/25 vs. VI 25				
Study 373	Day 169	95	60, 130	<0.001
Study 360	Day 169	90	39, 142	<0.001
Study 417	Week 12	111	62, 161	<0.001 [a]
Study 418	Week 12	132	81, 183	<0.001
Contribution of VI 25: Comparison of UMEC/VI 62.5/25 vs. UMEC 62.5				
Study 373	Day 169	52	17, 87	0.004
Study 417	Week 12	124	67, 181	<0.001 [a]
Study 418	Week 12	99	41, 157	<0.001

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; UMEC=umeclidinium bromide; VI=vilanterol
Note: The individual Primary Efficacy Studies were powered for the comparisons presented in this table. The individual Exercise/Lung Function Studies were not powered for the comparisons presented in this table and are considered supportive of the powered comparisons.
a. p-values are nominal for this comparison according to the terms of the testing hierarchy for study 417.

Figure 34 Contribution of UMEC 62.5 mcg and VI 25 mcg to the Efficacy of UMEC/VI 62.5/25 mcg for Trough FEV_1 (mL) at Day 169



Abbreviations: UMEC=umeclidinium bromide; VI=vilanterol
Note: Treatment difference is for LS mean change from baseline in trough FEV_1 at Day 169. The individual Primary Efficacy Studies were powered for the comparisons presented in this figure. The individual Exercise/Lung Function Studies were not powered for the comparisons presented in this figure and are considered supportive of the powered comparisons.

4.7. Clinical Efficacy Conclusions

The results of the Phase III trials provide substantial evidence for the efficacy of UMEC/VI 62.5/25 mcg once daily as a maintenance therapy for the treatment of COPD. UMEC/VI 62.5/25 mcg demonstrated clinically meaningful and sustained improvements in lung function compared with placebo, UMEC 62.5, VI 25 mcg, and tiotropium. Both components, UMEC 62.5 mcg and VI, were shown to contribute to the efficacy of UMEC/VI 62.5/25 mcg and the efficacy of the components was confirmed by demonstrating statistically significant greater improvements in the primary and secondary measures of trough FEV_1 and 0 to 6 hour weighted mean FEV_1, respectively, compared with placebo. UMEC/VI 62.5/25 mcg and 125/25 mcg had similar efficacy, supporting selection of the 62.5/25 mcg dose for approval as no clear benefit was obtained with the higher dose.

The benefit of UMEC/VI 62.5/25 mcg on symptoms and health-related quality of life was supported by clinically meaningful reductions in rescue albuterol use and improvements in SGRQ total scores and TDI focal and SOBDA scores compared with placebo.

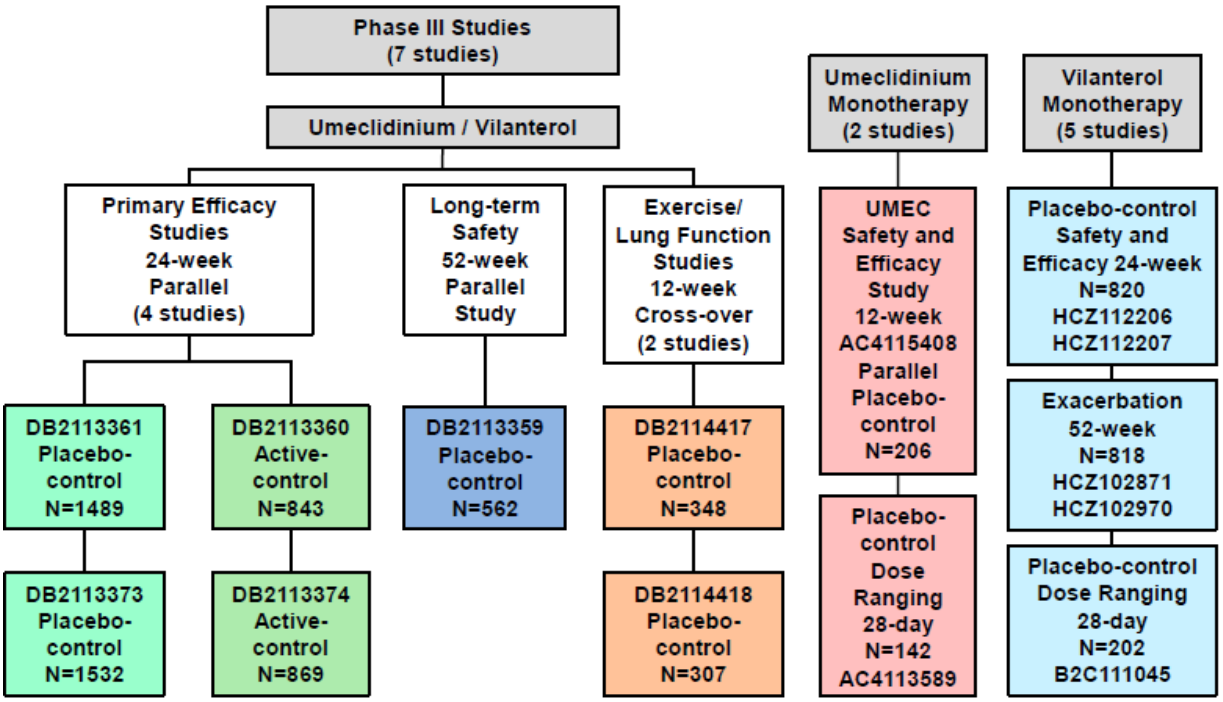
Overall, UMEC/VI 62.5/25 was shown to be an efficacious treatment for a broad population of patients with COPD, producing improvements in key measures considered important to the treatment of COPD.

5. CLINICAL SAFETY

5.1. Overview of Clinical Safety Evaluations

The safety of UMEC/VI and the individual components in COPD was evaluated from a comprehensive database of a total of 14 clinical studies with treatment periods of at least 4 weeks and a relevant UMEC/VI, UMEC or VI treatment group (All COPD Studies Grouping) (Figure 35). The objectives, design, enrollment criteria, treatment groups, and numbers of subjects by treatment group are tabulated in Appendix 10.4 for each of these studies.

Figure 35 All COPD Studies Grouping: Clinical Studies in COPD Subjects with Treatment Periods of at Least 4 Weeks and a Relevant Treatment Group



Note: Ns represent all subjects in relevant treatment arms (Intent-to-treat population).

Exposure data, an overview of AEs, and deaths are reported for integrated data from all 14 studies in the All COPD Studies Grouping.

Integrated data from the four 24-week Primary Efficacy Studies underpin the safety conclusions supporting the use of UMEC/VI in the treatment of COPD. Data on the long-term safety of UMEC and UMEC/VI are provided from the 52-week Long-term Safety Study. The VI 25 mcg monotherapy long-term safety data from COPD studies HZC102871 and HZC102970 (study 871

and study 970, respectively) were reviewed as part of the BREO ELLIPTA NDA submission which has been approved by the FDA. These data are not presented in this briefing document.

The following safety presentations are included for the Primary Efficacy Studies and the Long-term Safety Study: an overview of AEs, adjudicated deaths, adjudicated nonfatal serious adverse reports (SARs), AEs leading to withdrawal, frequently reported AEs, AESIs, 12-lead ECGs, vital signs, and clinical laboratory evaluations. Additionally, Holter ECG data are provided from the TFH subset of subjects in the placebo-controlled Primary Efficacy Studies (studies 373 and 361) and from the Long-term Safety Study.

Results are also presented from an external, blinded, independent adjudication process of all on-treatment and post-treatment deaths and serious adverse reports. This adjudication process which was undertaken to categorize events as respiratory- and CV-related deaths and hospitalizations. The 7 Phase III studies in the UMEC/VI COPD clinical development program and the Phase III study with UMEC monotherapy (Study 408), each of which included treatment periods of at least 12 weeks duration and a UMEC/VI or UMEC treatment group were included in the process:

- 4 Primary Efficacy Studies,
- 2 Exercise/Lung Function Studies
- Long-term Safety Study, and
- Study 408

The adjudication was carried out on the case/report as a whole (SAR). Thus, the case was adjudicated on the primary SAE (i.e., the event of the greatest medical significance), not on every event comprising a particular case. Adjudicated deaths were categorized as CV, respiratory, cancer, other cause of death, or unknown. Nonfatal SARs were categorized as CV, respiratory, other, or unknown. A more detailed description of the adjudication process is provided in Appendix 10.5. Adjudicated deaths and nonfatal SARs are presented for the integrated Primary Efficacy Studies, the integrated Exercise/Lung Function Studies, the Long-term Safety Study, and Study 408.

Specific pharmacologic LAMA and LABA class effects were assessed in all Phase III studies in the UMEC/VI COPD clinical development program through an evaluation of certain pre-specified AESIs. In addition, as pneumonia and LRTIs are commonly reported in patients with COPD, these events were also assessed in the UMEC/VI COPD program. The AESI groups are described in Appendix 10.6. Data on the occurrence of AESIs are reported for the Primary Efficacy Studies and Long-term Safety Study as these studies form the majority of the safety database.

Because CV effects have been associated with both classes of long-acting bronchodilators, a comprehensive evaluation of potential CV risk was undertaken. This evaluation includes:

- MACE analyses based on integrated data from all 8 studies included in the adjudication process,

- A focused presentation on CV AESI reports and 12-lead and 24-hour Holter ECGs for the Primary Efficacy Studies and the Long-term Safety Study, and
- Results of a thorough QT study.

Vital signs and clinical laboratory evaluations data are also presented for the integrated Primary Efficacy Studies and the Long-term Safety Study.

5.2. Extent of Exposure

5.2.1. All COPD Studies

The clinical exposure numbers shown in Table 47 are consistent with ICH E1 guidance [ICH E1] (300 subjects exposed for a minimum of 6 months and 100 subjects exposed for a minimum of 1 year). The numbers of subjects in each treatment group and total number of subjects are provided by study grouping or individual study in Table 48.

A total of 8138 subjects received at least one dose of study medication; 2454 subjects (980.73 subject-years) were exposed to UMEC/VI. Data following long-term exposure to UMEC 125/25 mcg and UMEC 125 mcg are used to support the evaluation of safety for UMEC/VI 62.5/25 mcg and UMEC 62.5 mcg.

Table 47 Summary of Exposure (All COPD Studies Grouping)

	Placebo N=1637	UMEC/VI 62.5/25 N=1124	UMEC/VI 125/25 N=1330	UMEC 62.5 N=576	UMEC 125 N=1087	VI 25 N=2501	TIO N=423
Exposure (days)							
n	1637	1124	1330	576	1087	2501	423
Mean	119.3	132.6	157.3	128.3	152.7	185.7	149.5
SD	77.85	49.33	87.71	50.62	97.48	112.78	45.75
Median	110.0	166.0	167.0	165.0	166.0	168.0	167.0
Min.	1	1	1	1	1	1	1
Max.	372	177	371	179	375	384	176
Total Subject-years Exposure	534.77	408.05	572.68	202.38	454.36	1271.25	173.09
Range of Exposure							
n	1637	1124	1330	576	1087	2501	423
>8 weeks	1251 (76)	1034 (92)	1212 (91)	522 (91)	900 (83)	2153 (86)	382 (90)
>12 weeks	1103 (67)	932 (83)	1129 (85)	450 (78)	827 (76)	2045 (82)	374 (88)
>20 weeks	783 (48)	705 (63)	869 (65)	341 (59)	670 (62)	1814 (73)	359 (85)
>24 weeks	394 (24)	326 (29)	462 (35)	154 (27)	370 (34)	1147 (46)	116 (27)
>48 weeks	66 (4)	NA	146 (11)	NA	133 (12)	590 (24)	NA

Abbreviations: COPD=chronic obstructive pulmonary disease; Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: Subjects in these cross-over studies may have received more than 1 treatment and are counted for each treatment received.

The UMEC/VI and UMEC monotherapy studies in COPD subjects provide the majority of exposure for all treatment groups except VI 25 mcg (Table 48). Exposure for VI 25 mcg monotherapy is from the Primary Efficacy Studies (N=1034) and Exercise/Lung Function

Studies (N=140) groupings as well as studies conducted as a part of the BREO ELLIPTA clinical development program (Studies 045, 206, 207, 871, and 970 [N=1327]). It is noteworthy that studies 871 and 970 (52-week studies) contributed 880 of the 1327 subjects who received VI in the BREO ELLIPTA program. Subjects in these 2 studies were required to have a documented history of at least 1 COPD exacerbation in the 12 months prior to Screening that required either systemic/oral corticosteroids, antibiotics, and/or hospitalization and therefore may represent a population with more severe COPD.

Table 48 Exposure by Study Grouping or Study (All COPD Studies Grouping)

	Number of Subjects							
Study Grouping/ Study Number	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO	Total Treated [a]
UMEC/VI Studies								
Primary Efficacy Studies								
361 373 360 374	555	842	832	418	629	1034	423	4733
Long-term UMEC/VI Safety Study								
359	109	NA	226	NA	227	NA	NA	562
Exercise/Lung Function Studies b,c								
417 418	321	282	272	89	91	140	NA	655
UMEC Monotherapy Studies								
408	68	NA	NA	69	69	NA	NA	206
589	71	NA	NA	NA	71	NA	NA	142
VI Monotherapy Studies								
Long-term VI Safety Studies								
871 970	NA	NA	NA	NA	NA	818	NA	818
Other VI Monotherapy Studies								
045	101	NA	NA	NA	NA	101	NA	202
206 207	412	NA	NA	NA	NA	408	NA	820
All COPD Studies	1637	1124	1330	576	1087	2501	423	8138

Abbreviations: COPD=chronic obstructive pulmonary disease; NA=not applicable; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

a. Number of subjects treated who received at least 1 dose of study drug.
b. Some subjects may have been enrolled in a previous study.
c. Subjects in these cross-over studies may have received more than 1 treatment and are counted for each treatment received.

5.2.2. Primary Efficacy Studies

Exposure to study medication by treatment groups is summarized for the Primary Efficacy Studies in Table 49.

Table 49 Summary of Exposure in the Primary Efficacy Studies (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Exposure (days), n	555	842	832	418	629	1034	423
Mean	136.6	150.1	147.6	146.7	144.5	145.3	149.5
SD	55.39	44.11	46.97	47.03	48.53	47.85	45.75
Median	167.0	168.0	168.0	168.0	167.0	168.0	167.0
Min	1	1	1	1	1	1	1
Max	192	177	179	179	183	206	176
Total Subject-years	207.52	345.92	336.27	167.88	248.89	411.20	173.09
Range of Exposure	Number (%) of Subjects						
n	555	842	832	418	629	1034	423
>8 weeks	468 (84)	774 (92)	747 (90)	377 (90)	558 (89)	927 (90)	382 (90)
>12 weeks	452 (81)	749 (89)	729 (88)	364 (87)	538 (86)	897 (87)	374 (88)
>20 weeks	405 (73)	705 (84)	684 (82)	341 (82)	498 (79)	822 (79)	359 (85)
>24 weeks	169 (30)	326 (39)	281 (34)	154 (37)	200 (32)	343 (33)	116 (27)

Abbreviations: Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

5.2.3. Long-term Safety Study

Exposure to study medication is summarized for study 359 in Table 50.

Table 50 Summary of Exposure (Study 359)

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Exposure (days), n	109	226	227
Mean	269.4	285.3	269.0
SD	127.54	114.18	125.52
Median	357.0	357.5	357.0
Min, Max	1, 372	1, 371	1, 375
Total Subject-years	80.39	176.50	167.20
Range of Exposure	Number (%) of Subjects		
n	109	226	227
>8 weeks	97 (89)	213 (94)	204 (90)
>12 weeks	95 (87)	211 (93)	202 (89)
>20 weeks	82 (75)	185 (82)	172 (76)
>24 weeks	82 (75)	181 (80)	170 (75)
>48 weeks	66 (61)	146 (65)	133 (59)

Abbreviations: Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol

5.3. Adverse Events

5.3.1. Overview of Adverse Events

Within each category of events for the All COPD Studies Grouping, the incidence of AEs was similar across all treatment groups including placebo and tiotropium (Table 51).

Table 51 Overall Summary of Adverse Events (All COPD Studies Grouping)

Category of Events	Placebo N=1637 SY=535	UMEC/VI 62.5/25 N=1124 SY=408	UMEC/VI 125/25 N=1330 SY=573	UMEC 62.5 N=576 SY=202	UMEC 125 N=1087 SY=454	VI [a] 25 N=2501 SY=1271	TIO N=423 SY=173
Incidence	Number (%) of Subjects						
Any on-treatment AEs	698 (43)	539 (48)	656 (49)	261 (45)	562 (52)	1367 (55)	208 (49)
Any fatal AEs [b, c]	5 (<1)	6 (<1)	1 (<1)	3 (<1)	7 (<1)	22 (<1)	2 (<1)
Any on-treatment SAEs [d]	65 (4)	57 (5)	66 (5)	29 (5)	61 (6)	225 (9)	22 (5)
Any AEs leading to permanent discontinuation of study drug or withdrawal from study [c,d]	97 (6)	60 (5)	71 (5)	34 (6)	68 (6)	151 (6)	20 (5)
Exposure-Adjusted Frequency	Number of Subjects with Events per 1000 Subject-Years						
Any on-treatment AEs	1305.2	1320.9	1145.5	1289.7	1236.9	1075.3	1201.7
Any fatal AEs [b, c]	9.3	14.7	1.7	14.8	15.4	17.3	11.6
Any on-treatment SAEs [c]	121.5	139.7	115.2	143.3	134.3	177.0	127.1
Any AEs leading to permanent discontinuation of study drug or withdrawal from study [c,d]	181.4	147.0	124.0	168.0	149.7	118.8	115.5

Abbreviations: AE=adverse event; SAE=serious adverse event; SY=subject-years; UMEC=umeclidinium bromide; VI=vilanterol

a. See Section 5.2.1 for a discussion of the composition of subjects in the VI treatment arm from various studies including studies from the BREO ELLIPTA program.
b. An additional post-treatment death was reported after study closure for a subject in the placebo group of study 373.
c. Includes both on-treatment and post-treatment AEs.
d. Includes fatal and nonfatal events.

In the Primary Efficacy Studies, approximately half of the subjects reported at least 1 on-treatment AE in each treatment group including placebo and tiotropium. For all AEs as well as for each category of AEs, the incidences were similar between the UMEC, VI, and UMEC/VI treatment groups compared with placebo (Table 52).

Table 52 Overall Summary of Adverse Events (Integrated Primary Efficacy Studies 361, 373, 360, 374)

Category of Events	Number (%) of Subjects						
	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Any on-treatment AE	264 (48)	447 (53)	438 (53)	216 (52)	348 (55)	518 (50)	208 (49)
Any fatal AE [a,b]	2 (<1)	5 (<1)	1 (<1)	3 (<1)	2 (<1)	6 (<1)	2 (<1)
Any adjudicated fatal SAR [b]	3 (<1)	5 (<1)	1 (<1)	3 (<1)	2 (<1)	6 (<1)	2 (<1)
Any on-treatment nonfatal SAE	24 (4)	47 (6)	43 (5)	27 (6)	35 (6)	35 (5)	20 (5)
Any adjudicated nonfatal SAR [b]	25 (5)	49 (6)	45 (5)	27 (6)	37 (6)	57 (6)	20 (5)
Any AE leading to permanent discontinuation of study drug or withdrawal from study [b,c]	26 (5)	50 (6)	47 (6)	31 (7)	41 (7)	59 (6)	20 (5)

Abbreviations: AE=adverse event; SAE=serious adverse event; SAR=serious adverse report; UMEC=umeclidinium bromide; VI=vilanterol

a. Additionally, a post-treatment death was reported after study closure for a subject in the placebo group of study 373.
b. Includes both on-treatment and post-treatment AEs.
c. Includes fatal and nonfatal events.

In study 359, at least 1 on-treatment AE was reported by 53% and 58% of subjects in the UMEC/VI 125/25 mcg and UMEC 125 mcg treatment groups compared with 52% for placebo (Table 53). The incidence of fatal events was higher in the UMEC 125 mcg treatment group (2%, 4 subjects) compared with placebo (<1%, 1 subject). The incidence of any adjudicated nonfatal SAR was similar across all treatment groups including placebo. Adverse events leading to permanent discontinuation or withdrawal were reported at a lower incidence in the UMEC/VI 125/25 mcg and UMEC 125 mcg treatment groups (8% and 9%, respectively) compared with placebo (12%).

Table 53 Overall Summary of Adverse Events (Study 359)

Category of Events	Number (%) of Subjects		
	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Any on-treatment AEs	57 (52)	120 (53)	132 (58)
Any fatal AE [a,b]	1 (<1)	0	4 (2)
Any adjudicated fatal SAR [a]	1 (<1)	0	4 (2)
Any on-treatment nonfatal SAE	7 (6)	14 (6)	15 (7)
Any adjudicated nonfatal SAR [a]	7 (6)	14 (6)	15 (7)
Any AE leading to permanent discontinuation of study treatment or withdrawal from study [a,b]	13 (12)	17 (8)	21 (9)

Abbreviations: AE=adverse event; SAE=serious adverse event; SAR=serious adverse report; UMEC=umeclidinium bromide; VI=vilanterol

a. Includes both on-treatment and post-treatment AEs.
b. Includes fatal and nonfatal events.

5.3.2. Adjudicated Deaths

This section includes the results of the adjudication process conducted by an external, independent, blinded adjudication committee for all fatal SARs. The adjudication was conducted to categorize all respiratory- and CV-related deaths occurring in the studies. For each fatal SAR, the Adjudication Committee members categorized the primary cause of death to 1 of the following pre-specified categories, (*i*) CV (sudden death, myocardial infarction, congestive heart failure, stroke or other CV cause; stroke was further categorized as haemorrhagic, thrombo-embolic or indeterminate), (*ii*) Respiratory (COPD exacerbation with or without pneumonia, pneumonia without COPD exacerbation, asthma, pulmonary embolism, other respiratory cause), (*iii*) Cancer (Lung Cancer, Unknown Primary, Other Cancer), (*iv*) Other, (*v*) Unknown (inadequate information or indeterminate). The adjudication process is described further in Appendix 10.5 (including all possible categories and subcategories).

The adjudication committee members reviewed each fatal case as a whole and assigned the primary cause of death to a category (e.g., cardiovascular, any type) and subcategory (e.g., sudden death). The adjudication subcategories may not correspond to MedDRA PTs or AESI subcategories which are comprised of events in selected MedDRA SMQs and/or individual PTs. An event adjudicated by the committee may fall under a different category than that reported by the investigator.

5.3.2.1. Primary Efficacy Studies

Adjudicated deaths included the 21 fatal events reported in the Primary Efficacy Studies and the post-treatment death reported after study closure for a subject in the placebo group of study 373. The incidence of adjudicated fatal SARs was <1% for all categories across all treatment groups (Table 54). No treatment or dose-related pattern was identified for adjudicated deaths either overall or by adjudicated categories and subcategories.

Table 54 Adjudicated Deaths (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

Fatal Serious Adverse Report Category Subcategory (Where Applicable)	Number (%) of Subjects Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Any fatal serious adverse report	3 (<1)	5 (<1)	1 (<1)	3 (<1)	2 (<1)	6 (<1)	2 (<1)
Cardiovascular – any type	1 (<1)	2 (<1)	0	0	0	2 (<1)	0
Sudden death	1 (<1)	1 (<1)	0	0	0	0	0
Myocardial infarction/ischemic heart disease	0	0	0	0	0	1 (<1)	0
Congestive heart failure	0	0	0	0	0	1 (<1)	0
Stroke – haemorrhagic	0	1 (<1)	0	0	0	0	0
Respiratory – any type	1 (<1)	2 (<1)	0	1 (<1)	0	1 (<1)	0
COPD exacerbation without evidence of pneumonia	1 (<1)	2 (<1)	0	1 (<1)	0	1 (<1)	0
Cancer – any type	0	0	0	0	2 (<1)	1 (<1)	0
Lung cancer	0	0	0	0	1 (<1)	0	0
Unknown primary	0	0	0	0	0	1 (<1)	0
Other cancer cause	0	0	0	0	1 (<1)	0	0
Other – any type	0	0	1 (<1)	1 (<1)	0	0	1 (<1)
Unknown – any type	1 (<1)	1 (<1)	0	1 (<1)	0	2 (<1)	1 (<1)
Inadequate information	1 (<1)	1 (<1)	0	1 (<1)	0	0	0
Indeterminate	0	0	0	0	0	2 (<1)	1 (<1)

Abbreviations: AESI=adverse event of special interest; COPD=chronic obstructive pulmonary disease; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

5.3.2.2. Long-term Safety Study

In study 359, there were no deaths in the UMEC/VI 125/25 mcg treatment group (Table 55). The incidence of adjudicated fatal SARs attributed to respiratory (<1%) or cancer (1%) categories was higher in the UMEC 125 mcg group compared with the placebo group in which there were no fatal SARs assigned to either the respiratory or cancer categories. The incidence of CV events was similar in the UMEC 125 mcg and placebo groups (both <1%, 1 subject). The higher number of fatal events in the UMEC 125 mcg group compared with the UMEC/VI 125/25 mcg and placebo groups was driven mainly by the 3 deaths attributed to cancer. There was no pattern to the type of cancer (metastases to spine [duration of UMEC exposure: 5 months], metastases to liver [duration of UMEC exposure: 4 days], and mediastinal neoplasm [duration of UMEC exposure: 1 year]) reported in these subjects.

Table 55 Adjudicated Fatal Serious Adverse Reports (Study 359)

Fatal Serious Adverse Report Category Subcategory (Where Applicable)	Number (%) of Subjects		
	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Any fatal serious adverse report	1 (<1)	0	4 (2)
Cardiovascular – any type	1 (<1)	0	1 (<1)
Myocardial infarction/ischemic heart disease	1 (<1)	0	0
Congestive heart failure	0	0	1 (<1)
Respiratory – any type	0	0	1 (<1)
COPD exacerbation with evidence of pneumonia	0	0	1 (<1)
Cancer – any type	0	0	3 (1)
Unknown primary	0	0	3 (1)
Other – any type	0	0	0
Unknown – any type	0	0	0

Abbreviations: AESI=adverse event of special interest; COPD=chronic obstructive pulmonary disease; UMEC=umeclidinium bromide VI=vilanterol

Note: One death in the UMEC 125 mcg group was reported in both the respiratory and cancer categories.

5.3.2.3. Exercise/Lung Function Studies

In the Exercise/Lung Function Studies, one subject (<1%) in the UMEC 125 mcg treatment group had an adjudicated fatal SAR categorized as unknown due to inadequate information. An additional subject (<1%) in the UMEC/VI 62.5/25 mcg treatment group had an adjudicated nonfatal SAR which was categorized as 'Other: lung cancer with brain metastasis' and the subject subsequently died following the adjudication.

5.3.2.4. Study 408

No deaths were reported during study 408.

5.3.3. Fatal Adverse Events: All COPD Studies

In the All COPD Studies Grouping, 46 of 8138 subjects had a fatal event (<1% across all treatment groups) (Table 56). This incidence of mortality was not unexpected in a population of patients with moderate to very severe COPD and the reported events were those that commonly occur in an older population or that are frequently seen in subjects with COPD.

Table 56 Summary of On-treatment or Post-treatment Fatal Adverse Events (All COPD Studies)

	Number (%) of Subjects						
System Organ Class Preferred Term	Placebo N=1637	UMEC/VI 62.5/25 N=1124	UMEC/VI 125/25 N=1330	UMEC 62.5 N=576	UMEC 125 N=1087	VI [a] 25 N=2501	TIO N=423
Any fatal AE	5 (<1)	6 (<1) [b]	1 (<1)	3 (<1) [b]	7 (<1) [b]	22 (<1) [b]	2 (<1)
Cardiac disorders							
Any event	2 (<1)	2 (<1)	0	0	1 (<1)	7 (<1)	0
Cardiac failure acute	0	0	0	0	1 (<1)	1 (<1)	0
Myocardial infarction	0	1 (<1)	0	0	0	1 (<1)	0
Acute coronary syndrome	0	0	0	0	0	1 (<1)	0
Acute myocardial infarction	0	0	0	0	0	1 (<1)	0
Arrhythmia	0	0	0	0	0	1 (<1)	0
Cardiac arrest	0	1 (<1)	0	0	0	0	0
Cardiac failure	0	0	0	0	0	1 (<1)	0
Cardio-respiratory arrest	0	0	0	0	0	1 (<1)	0
Cardiopulmonary failure	0	0	0	0	0	1 (<1)	0
Coronary artery insufficiency	1 (<1)	0	0	0	0	0	0
Myocardial ischaemia	1 (<1)	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders							
Any event	0	2 (<1)	0	1 (<1)	0	5 (<1)	1 (<1)
Chronic obstructive pulmonary disease	0	2 (<1)	0	1 (<1)	0	5 (<1)	0
Acute respiratory failure	0	0	0	1 (<1)	0	0	0
Respiratory arrest	0	0	0	0	0	0	1 (<1)
Respiratory failure	0	1 (<1)	0	0	0	0	0
General disorders and administration site conditions							
Any event	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	3 (<1)	0
Death	0	1 (<1)	0	0	1 (<1)	1 (<1)	0
Sudden death	1 (<1)	0	0	1 (<1)	0	1 (<1)	0
Sudden cardiac death	0	0	0	0	0	1 (<1)	0

System Organ Class Preferred Term	Number (%) of Subjects Placebo N=1637	UMEC/VI 62.5/25 N=1124	UMEC/VI 125/25 N=1330	UMEC 62.5 N=576	UMEC 125 N=1087	VI [a] 25 N=2501	TIO N=423
Neoplasms benign, malignant and unspecified (including cysts and polyps)							
Any event	0	1 (<1)	0	0	4 (<1)	2 (<1)	0
Lung neoplasm malignant	0	1 (<1)	0	0	0	1 (<1)	0
Metastases to bone	0	0	0	0	1 (<1)	1 (<1)	0
Metastases to central nervous system	0	1 (<1)	0	0	1 (<1)	0	0
Metastases to liver	0	0	0	0	1 (<1)	0	0
Metastases to spine	0	0	0	0	1 (<1)	0	0
Metastatic squamous cell carcinoma	0	0	0	0	0	1 (<1)	0
Non-small cell lung cancer	0	0	0	0	1 (<1)	0	0
Pancreatic carcinoma metastatic	0	0	0	0	1 (<1)	0	0
Infections and infestations							
Any event	1 (<1)	0	0	1 (<1)	1 (<1)	3 (<1)	0
Pneumonia	1 (<1)	0	0	0	1 (<1)	1 (<1)	0
Lower respiratory tract infection	0	0	0	0	0	1 (<1)	0
Peritonitis	0	0	0	1 (<1)	0	0	0
Respiratory tract infection	0	0	0	0	0	1 (<1)	0
Sepsis	0	0	0	0	0	1 (<1)	0
Gastrointestinal disorders							
Any event	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Upper gastrointestinal haemorrhage	0	0	1 (<1)	0	0	0	1 (<1)
Abdominal pain lower	0	0	0	0	0	1 (<1)	0
Vascular disorders							
Any event	1 (<1)	0	0	0	0	1 (<1)	0
Arteriosclerosis	1 (<1)	0	0	0	0	1 (<1)	0
Hepatobiliary disorders							
Any event	0	0	0	1 (<1)	0	0	0
Cholecystitis	0	0	0	1 (<1)	0	0	0
Immune system disorders							
Any event	0	0	0	0	0	1 (<1)	0
Anaphylactic reaction	0	0	0	0	0	1 (<1)	0
Injury, poisoning and procedural complications							
Any event	0	0	0	0	0	1 (<1)	0
Accidental poisoning	0	0	0	0	0	1 (<1)	0
Nervous system disorders							
Any event	0	1 (<1)	0	0	0	0	0
Haemorrhagic stroke	0	1 (<1)	0	0	0	0	0
Renal and urinary disorders							
Any event	0	0	0	0	0	1 (<1)	0
Renal failure acute	0	0	0	0	0	1 (<1)	0

Abbreviations: AE=adverse event; COPD=chronic obstructive pulmonary disease; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: An additional post-treatment death was reported after study closure for a subject in the placebo group of study 373.

a. See Section 5.2.1 for a discussion of the composition of subjects in the VI treatment arm from various studies including studies from the BREO ELLIPTA program.

b. More than 1 fatal AE was reported for some subjects in these treatment groups.

5.3.4. Adjudicated Nonfatal Serious Adverse Reports

As was described for adjudicated fatal SARs, this section includes the results of the adjudication process conducted by an external, independent, blinded adjudication committee for all nonfatal SAR narratives. For all non-fatal SARs, the Adjudication Committee members categorized the primary SAE to one of the pre-specified categories described in Section 5.3.2 for adjudicated deaths except that the category for cancer was not included for nonfatal SARs and "sudden death" was not included as a subcategory under the CV category in the nonfatal SAR adjudication. See Appendix 10.5 for a more detailed description of the process including all possible categories and subcategories.

5.3.4.1. Primary Efficacy Studies

No treatment or dose-related pattern was identified for adjudicated nonfatal SARs, either overall or by adjudicated category (Table 57). The respiratory category had the highest incidence of adjudicated nonfatal SARs; reported for 3% of subjects in the UMEC/VI 62.5/25 mcg and UMEC 62.5 mcg treatment groups, and 2% in each other treatment group. In each treatment group, the most common respiratory subcategory was COPD exacerbation without evidence of pneumonia, which ranged in incidence from <1% in the UMEC 125 mcg and tiotropium groups to 3% in the UMEC 62.5 mcg group.

Serious adverse reports categorized to CV causes had an incidence of 2% in the UMEC 125 mcg group and ≤1% in all other treatment groups, including the UMEC/VI 125/25 mcg treatment group.

The 'other' causes category comprised events that were not assessed as respiratory or CV in nature. "Other" causes were associated with primary SARs for 2% to 3% of subjects in all treatment groups. In addition, the sub-category of "Other Cardiovascular Cause" included reports adjudicated as CV-related but not adjudicated to the pre-defined CV sub-categories (e.g., arrhythmias, peripheral arterial disease and hypertension).

Table 57 Adjudicated Nonfatal Serious Adverse Reports (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

Serious Adverse Report Category Subcategory (Where Applicable)	Number (%) of Subjects						
	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Any serious adverse report	25 (5)	49 (6)	45 (5)	27 (6)	37 (6)	57 (6)	20 (5)
Cardiovascular – any type	2 (<1)	7 (<1)	8 (<1)	4 (<1)	11 (2)	13 (1)	2 (<1)
Myocardial infarction/ischemic heart disease	0	5 (<1)	3 (<1)	3 (<1)	4 (<1)	5 (<1)	0
Congestive heart failure	0	0	0	0	1 (<1)	1 (<1)	0
Stroke – any type	1 (<1)	0	0	0	1 (<1)	2 (<1)	0
Thromboembolic	1 (<1)	0	0	0	0	1 (<1)	0
Indeterminate	0	0	0	0	1 (<1)	1 (<1)	0
Other cardiovascular cause	1 (<1)	2 (<1)	5 (<1)	1 (<1)	5 (<1)	5 (<1)	2 (<1)
Respiratory – any type	13 (2) [a]	27 (3)	20 (2)	13 (3)	10 (2)	22 (2)	9 (2)
COPD exacerbation with evidence of pneumonia	3 (<1)	1 (<1)	2 (<1)	1 (<1)	3 (<1)	1 (<1)	2 (<1)
COPD exacerbation without evidence of pneumonia	9 (2)	21 (2)	13 (2)	12 (3)	4 (<1)	15 (1)	3 (<1)
Pneumonia/respiratory tract infection without COPD exacerbation	0	4 (<1)	2 (<1)	0	1 (<1)	4 (<1)	3 (<1)
Pulmonary embolism	0	0	0	0	1 (<1)	1 (<1)	0
Other respiratory cause	2 (<1)	1 (<1)	3 (<1)	0	1 (<1)	1 (<1)	1 (<1)
Other – any type	10 (2)	16 (2)	20 (2)	12 (3)	16 (3)	22 (2)	9 (2)
Unknown – any type	1 (<1)	0	1 (<1)	0	0	1 (<1)	0
Inadequate information	0	0	1 (<1)	0	0	0	0
Indeterminate	1 (<1)	0	0	0	0	1 (<1)	0

Abbreviations: COPD=chronic obstructive pulmonary disease; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

a. Subject 6727 in study 361 reported 2 SAEs in the respiratory subgroup that were adjudicated independently.

5.3.4.2. Long-term Safety Study

In study 359, nonfatal SARs assigned to respiratory causes and CV causes had higher incidences in the placebo treatment group (3% and 2%, respectively) than in the UMEC/VI 125/25 mcg (2% and 1%, respectively) and UMEC 125 mcg treatment groups (2% and 1%, respectively). Most nonfatal SARs were categorized to the "other" causes category, 3% of subjects in the UMEC/VI 125/25 mcg and UMEC 125 mcg treatment groups, and 2% in the placebo treatment group (Table 58).

Table 58 Adjudicated Nonfatal Serious Adverse Reports (Study 359)

Serious Adverse Report Category – Subcategory (Where Applicable)	Number (%) of Subjects		
	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Any serious adverse report	7 (6)	14 (6)	15 (7)
Cardiovascular – any type	2 (2)	3 (1)	3 (1)
Myocardial infarction/ischemic heart disease	1 (<1)	2 (<1)	2 (<1)
Congestive heart failure	1 (<1)	0	0
Other cardiovascular cause	1 (<1)	1 (<1)	1 (<1)
Respiratory – any type	3 (3)	4 (2)	5 (2)
COPD exacerbation with evidence of pneumonia	0	0	1 (<1)
COPD exacerbation without evidence of pneumonia	3 (3)	2 (<1)	2 (<1)
Pneumonia/respiratory tract infection without COPD exacerbation	0	1 (<1)	1 (<1)
Other respiratory cause	0	1 (<1)	1 (<1)
Other – any type	2 (2)	7 (3)	7 (3)
Unknown – any type	1 (<1)	0	0
Indeterminate	1 (<1)	0	0

Abbreviations: COPD=chronic obstructive pulmonary disease; UMEC=umeclidinium bromide; VI=vilanterol

5.3.4.3. Exercise/Lung Function Studies

In the Exercise/Lung Function Studies, nonfatal SARs were assigned to respiratory causes in 2% of the VI 25 mcg group and ≤1% in the other groups. Less than 1% of subjects in each treatment group had a SAR categorized as CV in nature; UMEC/VI 125/25 mcg had no reports in this category. The "other" causes category (i.e., not CV or respiratory in nature) had the highest incidence of nonfatal SARs; 6% of subjects in the VI 25 mcg group, 3% in the UMEC 125 mcg group, 2% in the placebo and both UMEC/VI groups, and no reports categorized as "other" in the UMEC 62.5 mcg group (Table 59).

Table 59 Adjudicated Nonfatal Serious Adverse Reports (Studies 417 and 418)

Serious Adverse Report Category – Subcategory (Where Applicable)	Number (%) of Subjects					
	Placebo N=321	UMEC/VI 62.5/25 N=282	UMEC/VI 125/25 N=272	UMEC 62.5 N=89	UMEC 125 N=91	VI 25 N=140
Any serious adverse report	11 (3)	9 (3)	10 (4)	1 (1)	3 (3)	12 (9)
Cardiovascular – any type	3 (<1)	1 (<1)	0	0	0	1 (<1)
Myocardial infarction/ischemic heart disease	0	1 (<1)	0	0	0	1 (<1)
Stroke – any type	1 (<1)	0	0	0	0	0
Haemorrhagic	1 (<1)	0	0	0	0	0
Other cardiovascular cause	2 (<1)	0	0	0	0	0
Respiratory – any type	4 (1)	1 (<1)	4 (1)	1 (1)	0	3 (2)
COPD exacerbation with evidence of pneumonia	0	0	1 (<1)	0	0	0
COPD exacerbation without evidence of pneumonia	4 (1)	0	3 (1)	0	0	2 (1)
Pneumonia/respiratory tract infection without COPD exacerbation	0	0	0	0	0	1 (<1)
Pulmonary embolism	0	0	0	1 (1)	0	0
Other respiratory cause	0	1 (<1)	0	0	0	0
Other – any type	5 (2)	7 (2)	6 (2)	0	3 (3)	8 (6)
Unknown – any type	0	0	0	0	0	0

Abbreviations: COPD=chronic obstructive pulmonary disease; UMEC=umeclidinium bromide; VI=vilanterol

5.3.4.4. Study 408

In study 408, the 4 nonfatal SARs (1 each in the placebo and UMEC 62.5 mcg treatment groups, and 2 in UMEC 125 mcg treatment group) were distributed among CV (1 in the UMEC 125 mcg treatment group), respiratory (1 in each of the UMEC treatment groups), and "unknown" causes (1 in the placebo treatment group) with no dose- or treatment-related patterns either overall or by category (all <1%) (Table 60).

Table 60 Adjudicated Nonfatal Serious Adverse Reports (Study 408)

Serious Adverse Report Category – Subcategory (Where Applicable)	Number (%) of Subjects		
	Placebo N=68	UMEC 62.5 N=69	UMEC 125 N=69
Any serious adverse report	1 (1)	1 (1)	2 (3)
Cardiovascular – any type	0	0	1 (1)
Myocardial infarction/ischemic heart disease	0	0	1 (1)
Respiratory – any type	0	1 (1)	1 (1)
COPD exacerbation with evidence of pneumonia	0	0	1 (1)
Other respiratory cause	0	1 (1)	0
Other – any type	0	0	0
Unknown – any type	1 (1)	0	0
Indeterminate	1 (1)	0	0

Abbreviations: COPD=chronic obstructive pulmonary disease; UMEC=umeclidinium bromide

5.3.5. Adverse Events Leading to Withdrawal or Permanent Discontinuation of Study Drug

5.3.5.1. Primary Efficacy Studies

In the Primary Efficacy Studies, the incidence of AEs leading to withdrawal or permanent discontinuation of study drug (including on-treatment and post-treatment fatal, serious, and non-serious AEs) was low (5% to 7% in all treatment groups including placebo and tiotropium) and no pattern was discernible in the types of AEs that led to withdrawal or permanent discontinuation of study drug. The only AEs leading to permanent discontinuation or withdrawal of 1% or more of subjects in any treatment group were COPD (reported by 1% to 3% of subjects in the UMEC/VI or component treatment groups compared with 3% and <1% in the placebo and tiotropium groups, respectively) and pneumonia (reported by ≤1% of subjects in all treatment groups).

5.3.5.2. Long-term Safety Study

In study 359, the incidence of on-treatment AEs leading to permanent discontinuation of study drug or withdrawal (including on-treatment and post-treatment fatal, serious, and non-serious AEs) was 9% for the UMEC 125 mcg treatment group, 8% for the UMEC/VI 125/25 mcg treatment group, and 11% for placebo. The UMEC 125 mcg treatment group had a slightly higher incidence of AEs leading to withdrawal of ventricular extrasystoles (2%), SVT (1%), and sinus tachycardia (1%) compared with placebo (<1% for each event), however, this same pattern was not observed in the UMEC/VI 125/25 mcg treatment group. The incidences of individual AEs leading to permanent discontinuation of study drug or withdrawal in the UMEC 125/25 mcg treatment group were the same as or less than that reported for placebo.

5.3.6. Frequently Reported Adverse Events

5.3.6.1. Primary Efficacy Studies

No noteworthy differences across treatment groups were observed in the incidence of individual AEs reported by ≥3% of subjects in any treatment group (Table 61). The most commonly reported AEs were headache, nasopharyngitis, cough, upper respiratory tract infection (URTI) and back pain, all of which are common in the general COPD population.

Table 61 Summary of On-treatment Adverse Events Reported by 3% or More of Subjects Within Either UMEC/VI Treatment Group (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

	Number (%) of Subjects						
Preferred Term	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Any AE	264 (48)	447 (53)	438 (53)	216 (52)	348 (55)	518 (50)	208 (49)
Headache	58 (10)	76 (9)	75 (9)	32 (8)	62 (10)	87 (8)	24 (6)
Nasopharyngitis	48 (9)	74 (9)	77 (9)	29 (7)	43 (7)	98 (9)	33 (8)
Cough	23 (4)	18 (2)	44 (5)	16 (4)	29 (5)	37 (4)	11 (3)
URTI	21 (4)	27 (3)	24 (3)	21 (5)	23 (4)	32 (3)	22 (5)
Back pain	20 (4)	31 (4)	23 (3)	8 (2)	27 (4)	20 (2)	15 (4)

Abbreviations: AE=adverse event; COPD=chronic obstructive pulmonary disease; TIO=tiotropium; UMEC=umeclidinium bromide; URTI=upper respiratory tract infection; VI=vilanterol

5.3.6.2. Long-term Safety Study

In study 359, headache and nasopharyngitis were the most commonly reported AE across all 3 treatment groups (Table 62).

Table 62 Summary of On-treatment Adverse Events Reported by 3% or More of Subjects in the UMEC/VI Treatment Group (Study 359)

	Number (%) of Subjects		
Preferred Term	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Any AE	57 (52)	120 (53)	132 (58)
Headache	9 (8)	20 (9)	25 (11)
Nasopharyngitis	5 (5)	11 (5)	20 (9)
Ventricular extrasystoles	5 (5)	11 (5)	12 (5)
Extrasystoles	4 (4)	10 (4)	10 (4)
Back pain	3 (3)	10 (4)	9 (4)
Hypertension	5 (5)	8 (4)	4 (2)
Sinusitis	3 (3)	8 (4)	6 (3)
Influenza	5 (5)	6 (3)	5 (2)
Cough	1 (<1)	6 (3)	6 (3)

Abbreviations: AE=adverse event; UMEC=umeclidinium bromide; VI=vilanterol

5.3.7. Adverse Events in Subgroups

In the Primary Efficacy Studies, no clinically important differences in AE profiles were observed based on gender, age, or race.

5.3.8. Non-cardiovascular Adverse Events of Special Interest

5.3.8.1. Overall LAMA and LABA Adverse Events of Special Interest

Pharmacologic effects of LAMAs and LABAs were proactively assessed in the UMEC/VI COPD clinical development program through an evaluation of AESIs defined a priori for UMEC and/or VI, including CV effects (acquired long QT interval, cardiac arrhythmias, cardiac failure, cardiac ischaemia, hypertension, sudden death, and stroke), effects on glucose or potassium, tremor, urinary retention, ocular effects, gallbladder disorders, intestinal obstruction, and anticholinergic effects. Pneumonia was also included as an AESI because of its occurrence in patients with COPD. The pneumonia AESI group included AE terms for LRTI and pneumonia and is, therefore, referenced as the LRTI and Pneumonia AESI group. Cardiovascular AESIs are presented in Section 5.4.2.

Information on AESI groups and subgroups including the selection of AE terms included in this evaluation is given in Appendix 10.6. A particular set of search terms was specified for each AESI grouping. The AE search terms were based on SMQs and/or a selection of MedDRA PTs, which are not necessarily diagnostic but were chosen to assure that AE terms that may be associated with the safety concern of interest were evaluated.

There were no unexpected findings with regard to non-CV AESIs and no evidence of treatment-or dose-related effects in either the Primary Efficacy Studies or study 359 (Table 63 and Table 64, respectively).

Few events were reported in each treatment group for the individual AESI categories in both the Primary Efficacy Studies and the Long Term Safety Study (Table 63). The AESI groupings of anticholinergic effects and LRTI and pneumonia were the most common categories for reports of AESIs in the Primary Efficacy Studies and are further described in Section 5.3.8.2 and Section 5.3.8.3, respectively.

Table 63 Incidence of Non-Cardiovascular On-treatment AESIs (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

AESI Grouping	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Incidence	Number (%) of Subjects						
Anticholinergic effects	22 (4)	25 (3)	43 (5)	18 (4)	29 (5)	40 (4)	15 (4)
LRTI and pneumonia	8 (1)	26 (3)	23 (3)	6 (1)	22 (3)	14 (1)	17 (4)
Effects on glucose	2 (<1)	11 (1)	4 (<1)	7 (2)	11 (2)	17 (2)	6 (1)
Ocular effects	5 (<1)	7 (<1)	7 (<1)	3 (<1)	8 (1)	6 (<1)	1 (<1)
Tremor	2 (<1)	1 (<1)	0	3 (<1)	1 (<1)	1 (<1)	1 (<1)
Gallbladder disorders	1 (<1)	2 (<1)	0	3 (<1)	0	2 (<1)	0
Effects on potassium	1 (<1)	0	2 (<1)	0	1 (<1)	1 (<1)	1 (<1)
Urinary retention	0	1 (<1)	0	0	2 (<1)	1 (<1)	2 (<1)
Intestinal obstruction	2 (<1)	1 (<1)	0	0	0	0	0

Abbreviations: AESI=adverse events of special interest; LRTI=lower respiratory tract infection; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Table 64 Incidence of Non-Cardiovascular On-treatment AESIs (Study 359)

AESI Grouping	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Incidence	Number (%) of Subjects		
LRTI and pneumonia	2 (2)	5 (2)	11 (5)
Effects on glucose	0	8 (4)	1 (<1)
Anticholinergic effects	2 (2)	5 (2)	5 (2)
Ocular effects	1 (<1)	1 (<1)	1 (<1)
Effects on potassium	0	0	1 (<1)
Gallbladder disorders	0	0	2 (<1)
Urinary retention	0	0	0
Intestinal obstruction	0	0	0
Tremor	0	0	0

Abbreviations: AESI=adverse events of special interest; LRTI=lower respiratory tract infection; UMEC=umeclidinium bromide; VI=vilanterol

5.3.8.2. Anticholinergic Effects AESI Grouping

The incidence of individual on-treatment AESIs in the anticholinergic effects special interest group (anticholinergic syndrome SMQ) was ≤2% in each treatment group and similar across treatment groups in both the Primary Efficacy Studies and study 359 (Table 65 and

Table 66).

Table 65 On-treatment Anticholinergic Effects AESIs by Preferred Term (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

Anticholinergic Effects AESIs Preferred Term	Number (%) of Subjects						
	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Any term	22 (4)	25 (3)	43 (5)	18 (4)	29 (5)	40 (4)	15 (4)
Agitation	0	0	0	1 (<1)	0	0	0
Balance disorder	0	1 (<1)	0	0	0	0	0
Confusional state	0	0	1 (<1)	0	0	0	0
Delirium	0	0	0	0	1 (<1)	1 (<1)	0
Dizziness	8 (1)	10 (1)	10 (1)	3 (<1)	5 (<1)	11 (1)	2 (<1)
Dry eye	0	0	2 (<1)	0	0	0	1 (<1)
Dry mouth	2 (<1)	4 (<1)	14 (2)	3 (<1)	5 (<1)	6 (<1)	7 (2)
Dysphagia	1 (<1)	0	0	0	0	1 (<1)	0
Loss of consciousness	0	0	0	1 (<1)	2 (<1)	0	1 (<1)
Presyncope	0	0	0	1 (<1)	0	1 (<1)	0
Pyrexia	8 (1)	5 (<1)	14 (2)	3 (<1)	9 (1)	14 (1)	2 (<1)
Restlessness	0	1 (<1)	0	0	1 (<1)	0	0
Somnolence	0	0	1 (<1)	0	1 (<1)	0	0
Tachycardia	2 (<1)	2 (<1)	4 (<1)	5 (1)	2 (<1)	5 (<1)	1 (<1)
Urinary retention	0	1 (<1)	0	0	2 (<1)	1 (<1)	1 (<1)
Vision blurred	2 (<1)	0	2 (<1)	1 (<1)	1 (<1)	3 (<1)	0
Visual acuity reduced	0	2 (<1)	0	0	1 (<1)	0	0

Abbreviations: AESI=adverse event of special interest; MedDRA= Medical Dictionary for Regulatory Activities; SMQ=standard MedDRA query; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: All AE terms in the anticholinergic SMQ were included in this search.

Table 66 On-treatment Anticholinergic Effects AESIs by Preferred Term (Study 359)

Anticholinergic Effects AESIs	Number (%) of Subjects		
	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Any term	2 (2)	5 (2)	5 (2)
Dizziness	1 (<1)	2 (<1)	3 (1)
Dry mouth	1 (<1)	1 (<1)	1 (<1)
Pyrexia	0	2 (<1)	0
Vision blurred	0	0	1 (<1)

Abbreviations: AESI=adverse event of special interest; MedDRA= Medical Dictionary for Regulatory Activities; SMQ=standard MedDRA query; UMEC=umeclidinium bromide
Note: All AE terms in the anticholinergic SMQ were included in this search.

5.3.8.3. LRTI and Pneumonia Grouping

Lower respiratory tract infections and pneumonia are commonly reported in patients with COPD. In the UMEC/VI development program, the occurrence of pneumonia was collected as an

investigator-reported AE and no chest radiograph was required. The LRTI and Pneumonia AESI group included a broad array of AE terms associated with lower respiratory infections (e.g., bronchitis, LRTI) and bacterial pneumonia.

In the Primary Efficacy Studies, a higher incidence of LRTI and Pneumonia AESI events was reported for the UMEC/VI 125/25 mcg, UMEC/VI 62.5/25 mcg, UMEC 125 mcg and tiotropium (3-4%) treatment groups compared with placebo, UMEC 62.5 mcg and VI 25 mcg (1% in each treatment group). The PT of 'pneumonia', the most commonly reported AE term, was reported at a higher incidence in the UMEC/VI 125/25 mcg (1%), UMEC 125 mcg (1%), and tiotropium (1%) treatment groups compared to the other active treatment groups and placebo (all <1%). The incidence of serious 'pneumonia' was similar (0 to <1%) across all active treatment groups and placebo. No dose- or treatment-related patterns were identified in the incidence of individual on-treatment AEs in the LRTI and Pneumonia special interest group.

Table 67 Incidence of LRTI and Pneumonia On-treatment AESI by Preferred Term (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

	Number (%) of Subjects						
LRTI and Pneumonia AESI	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Preferred Term	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
Any term	8 (1)	26 (3)	23 (3)	6 (1)	22 (3)	14 (1)	17 (4)
Bronchitis	1 (<1)	6 (<1)	6 (<1)	1 (<1)	8 (1)	4 (<1)	5 (1)
Bronchopneumonia	0	0	0	0	0	1 (<1)	0
Infective exacerbation of chronic obstructive airways disease	0	2 (<1)	0	2 (<1)	0	1 (<1)	1 (<1)
Lobar pneumonia	0	1 (<1)	0	0	0	1 (<1)	0
Lower respiratory tract infection	2 (<1)	9 (1)	4 (<1)	1 (<1)	3 (<1)	1 (<1)	5 (1)
Lower respiratory tract infection viral	0	1 (<1)	0	0	0	0	0
Lung consolidation	0	0	1 (<1)	0	0	0	0
Lung infection	0	0	2 (<1)	0	0	0	0
Lung infection pseudomonal	0	0	0	1 (<1)	0	0	0
Mycobacterium test positive	0	0	0	1 (<1)	0	0	0
Pneumonia	4 (<1)	6 (<1)	10 (1)	1 (<1)	8 (1)	4 (<1)	5 (1)
Pneumonia primary atypical	0	0	0	0	1 (<1)	0	0
Rhinotracheitis	0	0	0	0	1 (<1)	0	0
Sinobronchitis	0	0	0	0	0	0	1 (<1)
Tracheitis	1 (<1)	2 (<1)	0	0	0	2 (<1)	0
Tuberculosis	0	0	0	0	1 (<1)	0	0

Abbreviations: AESI=adverse event of special interest; LRTI=lower respiratory tract infection; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

In study 359, a higher incidence of LRTI and Pneumonia AESI events was observed in the UMEC 125 mcg treatment group (5%) compared with UMEC 125/25 mcg (2%) and placebo (2%). The PT of 'pneumonia', the most commonly reported AE term in this grouping, was reported for 3% of subjects in the UMEC 125 mcg treatment group compared with no subjects in the UMEC/VI 125/25 mcg and placebo groups. The 'pneumonia' was reported as serious for 1% of the subjects in the UMEC/VI 125 mcg treatment group.

Table 68 Incidence of LRTI and Pneumonia On-treatment AESIs by Preferred Term (Study 359)

LRTI and Pneumonia AESI Preferred Term	Number (%) of Subjects Placebo N=109	 UMEC/VI 125/25 N=226	 UMEC 125 N=227
Any term	2 (2)	5 (2)	11 (5)
Bronchitis	2 (2)	2 (<1)	2 (<1)
Lobar pneumonia	0	1 (<1)	0
Lower respiratory tract infection	0	1 (<1)	3 (1)
Pneumonia	0	0	6 (3)
Pneumonitis	0	0	1 (<1)
Tracheitis	1 (<1)	0	0
Sinobronchitis	0	1 (<1)	0
Bronchitis viral	0	2 (<1)	1 (<1)

Abbreviations: AESI=adverse event of special interest; LRTI=lower respiratory tract infection; UMEC=umeclidinium bromide; VI=vilanterol

5.4. Evaluation of Potential Cardiovascular Risk

The COPD population as a whole commonly experience CV co-morbidities [Curkendall, 2006]. There were no specific exclusionary criteria regarding CV risk in the UMEC/VI Phase III studies. Exclusion of patients with clinically significant uncontrolled CV disease was based on the medical judgment of the study investigator and/or an abnormal and clinically significant ECG finding at screening. In the Primary Efficacy Studies and the Long-term Safety Study, the majority of subjects (55-68% in each treatment group) reported at least one CV risk factor (*e.g.* hypertension [46-59%] hyperlipidemia [23-28%] or diabetes [10-15%]), 18-35% reported a current cardiac disorder and approximately half (49%) of the subjects were current smokers (Table 26). The majority of subjects (51-61%) in in each treatment group in these studies also reported taking at least one CV medication, including antihypertensive medications and/or cholesterol-lowering agents. A similar profile was reported for subjects in the other studies included in the MACE analyses.

A broad array of assessments to evaluate potential CV risks was included as follows:

- MACE analyses,
- AE reporting with categorization and analysis of CV AESIs,
- ECGs and Holters, and
- Vital Signs

5.4.1. MACE Analysis

The criteria for the planned MACE analysis (broad analysis) were defined a priori as follows:

- Adjudicated CV deaths,

- Cardiac Ischaemia Special Interest AE Subgroup (broad array of AE terms; Myocardial Infarction SMQ and Other Ischaemic Heart Disease SMQ) excluding fatalities, and
- Stroke Special Interest AE Subgroup (Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ) excluding fatalities.

A more focused post-hoc MACE analysis (narrow analysis) was conducted which included adjudicated CV death and stroke, as described for the planned analysis, but did not include the broad array of terms specified for the cardiac ischaemic special interest subgroup in the planned analysis. Only events relating specifically to myocardial infarction (defined as the PTs of "myocardial infarction" and "acute myocardial infarction" and described as "myocardial infarction" events) were included.

For both the broad and narrow analyses, no evidence for an increase in MACE with UMEC/VI or the individual components compared with placebo was seen (Table 69). Total MACE events were equal to or less than that reported for placebo for all active treatments. The incidences of adjudicated CV deaths and nonfatal stroke were low and similar across all treatment groups including placebo. Of note, there were no CV deaths in the UMEC/VI 125/25 mcg treatment group.

In the broad MACE analysis, the incidence of nonfatal cardiac ischaemia AESI (Myocardial infarction SMQ and Other ischaemic heart disease SMQ) and exposure-adjusted frequency of subjects with events were similar across treatment groups. No dose- or treatment-related patterns were identified.

In the narrow MACE analysis, the incidence of non-fatal myocardial infarction (MedDRA PTs of myocardial infarction and acute myocardial infarction) was low (<1%) across all treatment groups, although small imbalances in exposure-adjusted frequency were observed between UMEC- and VI-containing treatment groups when compared with placebo and tiotropium. There was no obvious dose relationship or additive effect from the combination. Whether this represents a true effect is difficult to determine due to the small numbers.

Table 69 Major Adverse Cardiac Events: Broad and Narrow Analyses (Integrated Studies 361, 373, 360, 374, 417, 418, 359, and 408)

	Placebo N=1053 SY=369	UMEC/VI 62.5/25 N=1124 SY=408	UMEC/VI 125/25 N=1330 SY=573	UMEC 62.5 N=576 SY=202	UMEC 125 N=1016 SY=449	VI 25 N=1174 SY=441	TIO N=423 SY=173
Incidence	Number (%) of Subjects						
MACE composite (broad)	20 (2)	15 (1)	22 (2)	9 (2)	14 (1)	17 (1)	6 (1)
MACE composite (narrow)	7 (<1)	5 (<1)	6 (<1)	2 (<1)	7 (<1)	8 (<1)	1 (<1)
Cardiovascular death [a] (broad and narrow)	2 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)	0
Nonfatal stroke AESI [b] (broad and narrow)	4 (<1)	0	3 (<1)	1 (<1)	2 (<1)	4 (<1)	1 (<1)
Nonfatal cardiac ischaemia AESI [c] (broad)	14 (1)	13 (1)	19 (1)	8 (1)	11 (1)	12 (1)	5 (1)
Nonfatal myocardial infarction [d] (narrow)	1 (<1)	3 (<1)	3 (<1)	1 (<1)	4 (<1)	2 (<1)	0
Exposure-adjusted frequencies	Number of Subjects with Events per 1000 Subject-Years						
MACE composite (broad)	54.3	36.8	38.4	44.5	31.2	38.5	34.7
MACE composite (narrow)	19.0	12.3	10.5	9.9	15.6	18.1	5.8
Cardiovascular death [a] (broad and narrow)	5.4	4.9	0	0	2.2	4.5	0
Nonfatal stroke AESI [b] (broad and narrow)	10.9	0	5.2	4.9	4.5	9.1	5.8
Nonfatal cardiac ischaemia AESI [c] (broad)	38.0	31.9	33.2	39.5	24.5	27.2	28.9
Nonfatal myocardial infarction [d] (narrow)	2.7	7.4	5.2	4.9	8.9	4.5	0
Total MACE	Total Number of Events						
Total MACE, n (broad)	22	16	22	11	15	18	6
Total MACE, n (narrow)	8	5	6	2	7	8	1

Abbreviations: AESI=adverse event of special interest; ECG=electrocardiogram; MACE=major adverse cardiac event; MedDRA= Medical Dictionary for Regulatory Activities; SMQ=standard MedDRA query; SY=subject-years; PT=preferred term; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: The broad analysis was a priori and the narrow analysis was post-hoc.

a. Cardiovascular deaths were independently adjudicated (see Appendix 10.5).
b. The following MedDRA SMQs contributed to the nonfatal stroke AESI category: Central nervous system haemorrhages and cerebrovascular conditions SMQ.
c. The following MedDRA SMQs contributed to the cardiac ischaemia AESI category: Myocardial Infarction SMQ; Other Ischaemic Heart Disease SMQ.
d. The following MedDRA PTs contributed to myocardial infarction: myocardial infarction and acute myocardial infarction.

5.4.2. Cardiovascular Adverse Events of Special Interest

An evaluation of CV AESIs defined a priori for UMEC and/or VI, included acquired long QT interval, cardiac arrhythmias, cardiac failure, cardiac ischaemia, hypertension, sudden death, and stroke. The AE terms that were included in these searches were based on standardized MedDRA queries and/or a selection of MedDRA PTs which are not necessarily diagnostic but were chosen to assure that AE terms that may be associated with the safety concern of interest were evaluated.

Overall, no dose- or treatment-related patterns were identified in the incidence of AEs in CV AESI categories in the Primary Efficacy Studies (Table 70) or study 359 (Table 71). The most commonly reported CV AESI category in both study groupings was cardiac arrhythmias followed by hypertension. The incidence of atrial arrhythmia is discussed in Section 5.4.3.

The incidence of cardiac ischaemia was low (<1 to 2%) across all treatment groups in the Primary Efficacy Studies, although small imbalances in exposure-adjusted frequency were

observed between UMEC- and VI-containing treatment groups when compared with placebo and tiotropium. There was no obvious dose relationship or additive effect from the combination. . In study 359, both the incidence and exposure-adjusted frequency of cardiac ischaemia were lower in the UMEC/VI 125/25 and UMEC 125 mcg groups compared with placebo.

Notably, there were very few reports (<1%) of stroke, acquired long QT, or sudden death in either the Primary Efficacy Studies (Table 70) or study 359 (Table 71).

Table 70 Cardiovascular Special Interest Subgroup: On-treatment AESIs (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

Cardiovascular AESI Category	Placebo N=555 SY=208	UMEC/VI 62.5/25 N=842 SY=346	UMEC/VI 125/25 N=832 SY=336	UMEC 62.5 N=418 SY=168	UMEC 125 N=629 SY=249	VI 25 N=1034 SY=411	TIO N=423 SY=173
Incidence	Number (%) of Subjects						
Any Cardiovascular AESI	40 (7)	70 (8)	55 (7)	41 (10)	52 (8)	95 (9)	27(6)
Acquired long QT	0	0	2 (<1)	1 (<1)	0	0	0
Cardiac arrhythmias	18 (3)	24 (3)	19 (2)	20 (5)	20 (3)	46 (4)	9 (2)
Cardiac failure	6 (1)	11 (1)	11 (1)	7 (2)	7 (1)	12 (1)	5 (1)
Cardiac ischaemia	5 (<1)	11 (1)	12 (1)	7 (2)	5 (<1)	12 (1)	4 (<1)
Hypertension	11 (2)	25 (3)	17 (2)	12 (3)	21 (3)	29 (3)	11 (3)
Sudden death	0	0	0	0	0	1 (<1)	0
Stroke	2 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (<1)	1 (<1)
Exposure-adjusted frequency	Number of Subjects with Events per 1000 Subject-Years						
Any Cardiovascular AESI	192.7	202.4	163.6	244.2	208.9	231.0	156.0
Acquired long QT	0	0	5.9	6.0	0	0	0
Cardiac arrhythmias	86.7	69.4	56.5	119.1	80.4	111.9	52.0
Cardiac failure	28.9	31.8	32.7	41.7	28.1	29.2	28.9
Cardiac ischaemia	24.1	31.8	35.7	41.7	20.1	29.2	23.1
Hypertension	53.0	72.3	50.6	71.5	84.4	70.5	63.6
Sudden death	0	0	0	0	0	2.4	0
Stroke	9.6	2.9	3.0	6.0	4.0	7.3	5.8

Abbreviations: AESI=adverse event of special interest; SY=subject-years; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Table 71 Cardiovascular Special Interest Subgroup: On-treatment AESIs (Study 359)

Cardiovascular AESI Category	Placebo N=109 SY=80	UMEC/VI 125/25 N=226 SY=177	UMEC 125 N=227 SY=167
Incidence	Number (%) of Subjects		
Any Cardiovascular AESI	25 (23)	34 (15)	49 (22)
Acquired long QT	0	0	0
Cardiac arrhythmias	17 (16)	26 (12)	39 (17)
Cardiac failure	1 (<1)	2 (<1)	4 (2)
Cardiac ischaemia	4 (4)	4 (2)	4 (2)
Hypertension	7 (6)	8 (4)	6 (3)
Sudden death	0	0	0
Stroke	0	0	1 (<1)
Exposure-adjusted frequency	Number of Subjects with Events per 1000 Subject-Years		
Any Cardiovascular AESI	311.0	192.6	293.1
Acquired long QT	0	0	0
Cardiac arrhythmias	211.5	147.3	233.3
Cardiac failure	12.4	11.3	23.9
Cardiac ischaemia	49.8	22.7	23.9
Hypertension	87.1	45.3	35.9
Sudden death	0	0	0
Stroke	0	0	6.0

Abbreviations: AESI=adverse events of special interest; SY=subject-years; UMEC=umeclidinium bromide; VI=vilanterol

5.4.3. Atrial Arrhythmias

Evidence suggests that atrial arrhythmias may be a class effect of anticholinergics [Anthonisen, 2002 and CDER, 2012]. Therefore, a thorough evaluation of atrial arrhythmia findings was conducted in the UMEC/VI program. The focus for discussions in this section is on atrial fibrillation and supraventricular tachycardia. The summary is as follows:

- 12-lead ECG: clinically significant abnormalities reported as atrial fibrillation, atrial fibrillation with rapid response [rate >100bpm], or SVT.
- 24-hour Holter ECG: clinically significant abnormalities reported as atrial fibrillation, atrial fibrillation with rapid response [rate >100bpm], sustained SVT (>100bpm, >30beats).
- Adverse event reports in the supraventricular tachyarrhythmia and Arrhythmia Related Investigations, Signs and Symptoms MedDRA SMQs.

Overall, a low number of atrial arrhythmias were reported based on 12-lead ECGs, Holter ECGs, or AEs, of which some occurred with a higher incidence in active treatment groups compared to placebo. There was no additive effect with the combination over individual components. Few of these findings were reported as SAEs and none were fatal.

5.4.3.1. ECG Findings

A higher incidence of post-baseline ECG abnormalities for subjects with any abnormal, clinically significant ECG interpretation for abnormalities of atrial fibrillation, atrial fibrillation

with rapid ventricular response [rate >100bpm], or SVT was noted in the active treatment groups compared with placebo in both the Primary Efficacy Studies and study 359 (Table 72).

Table 72 Selected Atrial Arrhythmia ECG Findings from All Subjects with Any Abnormal Clinically Significant ECG Interpretation (Integrated Primary Efficacy Studies 361, 373, 360, and 374 and Study 359)

	Number (%) of Subjects						
Primary Efficacy Studies	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Baseline atrial arrhythmias							
n	555	842	832	418	629	1034	423
Atrial fibrillation (<100bpm)	1 (<1)	1 (<1)	6 (<1)	3 (<1)	2 (<1)	7 (<1)	1 (<1)
Atrial fibrillation with rapid ventricular response (rate >100bpm)	0	1 (<1)	0	0	0	0	0
Supraventricular tachycardia (>100/min)	0	0	0	0	2 (<1)	0	0
Post-baseline atrial arrhythmias							
n	555	842	832	417	629	1034	423
Atrial fibrillation (<100bpm)	1 (<1)	3 (<1)	8 (<1)	3 (<1)	2 (<1)	7 (<1)	1 (<1)
Atrial fibrillation with rapid ventricular response (rate >100bpm)	0	3 (<1)	2 (<1)	2 (<1)	3 (<1)	7 (<1)	2 (<1)
Supraventricular tachycardia (>100/min)	0	1 (<1)	1 (<1)	0	2 (<1)	2 (<1)	2 (<1)
Study 359	Placebo N=109		UMEC/VI 125/25 N=226		UMEC 125 N=227		
Baseline – atrial arrhythmias							
n	109		226		227		
Atrial fibrillation (<100bpm)	0		0		0		
Atrial fibrillation with rapid ventricular response (rate >100bpm)	0		0		0		
Supraventricular tachycardia (>100/min)	0		0		0		
Post-baseline - atrial arrhythmias							
n	109		226		227		
Atrial fibrillation (<100bpm)	0		1 (<1)		1 (<1)		
Atrial fibrillation with rapid ventricular response (rate >100bpm)	0		1 (<1)		2 (<1)		
Supraventricular tachycardia (>100/min)	0		0		0		

Abbreviations: ECG=electrocardiogram; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

There were few findings of atrial arrhythmias on Holter ECGs in either the Primary Efficacy Studies (studies 361 and 373) or study 359 (Table 73). Similar to the findings reported for 12-lead ECGs, some of these abnormalities were reported at a higher incidence in the active treatment groups compared with placebo. There were no reports of these abnormalities on screening Holter ECGs in either the Primary Efficacy Studies or study 359.

Table 73 Selected Atrial Arrhythmia Holter ECG Findings from All Subjects with Any Abnormal Clinically Significant Holter ECG Abnormality (Integrated Studies 361 and 373 [TFH Subset] and Study 359)

	Number (%) of Subjects					
Primary Efficacy Studies	Placebo N=73	UMEC/VI 62.5/25 N=53	UMEC/VI 125/25 N=55	UMEC 62.5 N=54	UMEC 125 N=53	VI 25 N=108
Screening atrial arrhythmias						
n	73	52	55	54	53	107
Atrial fibrillation	0	0	0	0	0	0
Atrial fibrillation with rapid ventricular response (rate >100bpm)	0	0	0	0	0	0
Sustained supraventricular tachycardia (>100bpm, >30beats)	0	0	0	0	0	0
Post-randomization atrial arrhythmias						
n	72	53	55	54	53	107
Atrial fibrillation	0	0	0	0	0	0
Atrial fibrillation with rapid ventricular response (rate >100bpm)	0	0	1 (2)	1 (2)	0	1 (<1)
Sustained supraventricular tachycardia (>100bpm, >30beats)	1 (1)	1 (2)	0	2 (4)	0	3 (3)
Study 359	Placebo N=109		UMEC/VI 125/25 N=226		UMEC 125 N=227	
Screening atrial arrhythmias						
n	109		226		227	
Atrial fibrillation	0		0		0	
Atrial fibrillation with rapid ventricular response (rate >100bpm)	0		0		0	
Sustained supraventricular tachycardia (>100bpm, >30beats)	0		0		0	
Post-randomization atrial arrhythmias						
n	90		206		198	
Atrial fibrillation	0		0		0	
Atrial fibrillation with rapid ventricular response (rate >100bpm)	2 (2)		1 (<1)		3 (2)	
Sustained supraventricular tachycardia (>100bpm, >30beats)	2 (2)		5 (2)		9 (5)	

Abbreviations: ECG=electrocardiogram; TFH=twenty-four hour; UMEC=umeclidinium bromide; VI=vilanterol.

5.4.3.2. Atrial Arrhythmia Adverse Events

Few subjects in either the Primary Efficacy Studies or study 359 had supraventricular tachyarrhythmias reported as AEs (Table 74 and Table 75). Some of these AEs were reported at a higher incidence in the active treatment groups compared with the placebo group.

Table 74 On-treatment AEs of Supraventricular Tachyarrhythmias (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

Supraventricular tachyarrhythmia SMQ Preferred Term	Placebo N=555 SY=208	UMEC/VI 62.5/25 N=842 SY=346	UMEC/VI 125/25 N=832 SY=336	UMEC 62.5 N=418 SY=168	UMEC 125 N=629 SY=249	VI 25 N=1034 SY=411	TIO N=423 SY=173
Incidence	Number (%) of Subjects						
Atrial fibrillation	0	3 (<1)	2 (<1)	2 (<1)	2 (<1)	7 (<1)	0
Atrial flutter	0	1 (<1)	0	0	0	0	0
Sinus tachycardia	0	0	2 (<1)	0	2 (<1)	2 (<1)	0
Supraventricular extrasystoles	0	4 (<1)	0	1 (<1)	1 (<1)	2 (<1)	1 (<1)
Supraventricular tachycardia	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Exposure-adjusted frequencies	Number of Subjects with Events per 1000 Subject-Years						
Atrial fibrillation	0	8.7	5.9	11.9	8.0	17.0	0
Atrial flutter	0	2.9	0	0	0	0	0
Sinus tachycardia	0	0	5.9	0	8.0	4.9	0
Supraventricular extrasystoles	0	11.6	0	6.0	4.0	4.9	5.8
Supraventricular tachycardia	4.8	0	3.0	6.0	0	2.4	5.8

Abbreviations: AESI=adverse event of special interest; ECG=electrocardiogram; MedDRA= Medical Dictionary for Regulatory Activities; PT=preferred term; SMQ=standard MedDRA query; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: The supraventricular tachyarrhythmia SMQ includes the following PTs: arrhythmia supraventricular, atrial fibrillation; atrial flutter, atrial parasystole, atrial tachycardia, supraventricular extrasystoles, supraventricular tachyarrhythmia;, ECG P wave inverted, electrocardiogram P wave abnormal, retrograde P-waves, sinus tachycardia, supraventricular tachycardia.

Table 75 On-treatment AEs of Supraventricular Tachyarrhythmias (Study 359)

Supraventricular tachyarrhythmia SMQ Preferred Term	Placebo N=109 SY=80	UMEC/VI 125/25 N=226 SY=177	UMEC 125 N=227 SY=167
Incidence	Number (%) of Subjects		
Atrial fibrillation	2 (2)	1 (<1)	3 (1)
Sinus tachycardia	1 (<1)	0	6 (3)
Supraventricular extrasystoles	1 (<1)	1 (<1)	6 (3)
Supraventricular tachycardia	1 (<1)	2 (<1)	6 (3)
Exposure-adjusted frequencies	Number of Subjects with Events per 1000 Subject-Years		
Atrial fibrillation	24.9	5.7	17.9
Sinus tachycardia	12.4	0	35.9
Supraventricular extrasystoles	12.4	5.7	35.9
Supraventricular tachycardia	12.4	11.3	35.9

Abbreviations: AESI=adverse event of special interest; ECG=electrocardiogram; UMEC=umeclidinium bromide; VI=vilanterol
Note: The supraventricular tachyarrhythmia SMQ includes the following PTs: arrhythmia supraventricular, atrial fibrillation; atrial flutter, atrial parasystole, atrial tachycardia, supraventricular extrasystoles, supraventricular tachyarrhythmia;, ECG P wave inverted, electrocardiogram P wave abnormal, retrograde P-waves, sinus tachycardia, supraventricular tachycardia.

5.4.4. Cardiac Monitoring

5.4.4.1. 12-Lead ECGs

Post-dose 12-lead ECG data were obtained from 4732 subjects in the Primary Efficacy Studies and 562 subjects in study 359. Overall, a total of 43279 12-lead ECGs were obtained in the Primary Efficacy Studies and 9082 were obtained in study 359.

In the Primary Efficacy Studies, ECG measurements were taken at Screening; at Days 1, 84, and 168 (predose and 10 and 45 minutes postdose); and at the Early Withdrawal Visit, if applicable. In study 359, ECG measurements were taken at Screening; at Day 1 and Days 28, 91, 182, 273, and 364 (predose and 10 and 45 minutes postdose); and at the Early Withdrawal Visit, if applicable. All ECG measurements were obtained with standardized equipment provided by an external vendor.

ECG data were electronically transmitted to an independent cardiologist blinded to treatment assignment, who was responsible for providing measurements of QT intervals, PR intervals, HR and the ECG interpretations.

A discussion of 12-lead ECG findings related to atrial arrhythmias is provided in Section 5.4.3.1.

QTc(F) Interval, PR Interval, and Heart Rate

No clinically significant or treatment-related effects on QTc(F), PR interval or HR were observed in the Primary Efficacy Studies or study 359. The QTc findings from these studies were confirmed in a thorough QT study described in Section 5.4.4.3.

Primary Efficacy Studies

Least squares mean changes from baseline were small across all treatment groups for QTc(F) (-1.8 to 2.3 milliseconds), PR interval (-1.2 to 1.9 milliseconds), and HR (-5.4 to 2.9 bpm). The changes from baseline in these parameters were not considered clinically relevant and were similar across treatment groups at all time points.

Mean maximal post-baseline QTc(F) change from baseline was between 13.2 and 14.4 milliseconds in the UMEC/VI, UMEC, and VI treatment groups compared with 12.1 and 13.5 milliseconds in the placebo and tiotropium treatment groups, respectively.

Most subjects (91 to 95% across treatment groups) had maximum post-baseline QTc(F) values ≤450 milliseconds (Table 76). The majority of changes from baseline across all treatment groups (75% to 79%) were within the range of ≥0 to <30 milliseconds.

Table 76 Categorical Summary of Frequency of Change from Baseline QTc(F) (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

	Number (%) of Subjects						
	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Categories: Maximum Post-baseline [a, b] (msec)							
n	555	842	832	417	629	1034	423
≤450	518 (93)	790 (94)	761 (91)	394 (94)	591 (94)	974 (94)	402 (95)
>450 to ≤480	35 (6)	49 (6)	66 (8)	23 (6)	37 (6)	57 (6)	19 (4)
>480 to ≤500	2 (<1)	2 (<1)	5 (<1)	0	1 (<1)	2 (<1)	2 (<1)
>500	0	1 (<1)	0	0	0	1 (<1)	0
Change from Baseline Categories: Maximum Post-baseline [a, b] (msec)							
n	555	842	832	417	629	1034	423
<-60	0	0	0	0	0	0	0
≥-60 to <-30	0	1 (<1)	0	0	0	0	0
≥-30 to <0	82 (15)	98 (12)	96 (12)	54 (13)	74 (12)	114 (11)	52 (12)
≥0 to <30	421 (76)	633 (75)	643 (77)	319 (76)	492 (78)	818 (79)	322 (76)
≥30 to <60	50 (9)	108 (13)	92 (11)	43 (10)	62 (10)	98 (9)	48 (11)
≥60	2 (<1)	2 (<1)	1 (<1)	1 (<1)	1 (<1)	4 (<1)	1 (<1)

Abbreviations: msec=millisecond; QTc(F)=QT interval corrected for heart rate by Fridericia's formula; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

a. Baseline was the most recent recorded value before dosing on Day 1. For the majority of subjects, this was their predose value on Day 1.

b. Includes scheduled, unscheduled, and Early Withdrawal visits.

Long-term Safety Study

Similar to the Primary Efficacy Studies, LS mean changes from baseline were small across treatment groups for QTc(F) (-4.2 to 2.5 milliseconds), PR interval (-5.1 to 1.5 milliseconds), and HR (-6.3 to 1.5 bpm). The changes from baseline in these parameters were not considered clinically relevant and were similar across treatment groups at all time points.

Mean maximal post-baseline QTc(F) change from baseline was 18.4, 16.9, and 15.6 milliseconds for the UMEC/VI 125/25 mcg, UMEC 125 mcg, and placebo groups, respectively.

Most subjects (90 to 91% across treatment groups) reported maximum post-baseline QTc(F) values ≤450 milliseconds (Table 77). The majority of changes from baseline across all treatment groups (71% to 78%) were within the range of ≥0 to <30 milliseconds (Table 77).

Table 77 Maximum Post-Baseline QTc(F) Frequencies and Change from Baseline to Maximum (Study 359)

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Maximum Post-baseline [a, b]	Number (%) of Subjects		
≤450 msec	99 (91)	204 (90)	207 (91)
>450 to ≤480 msec	9 (8)	22 (10)	20 (9)
>480 to ≤500 msec	1 (<1)	0	0
>500 msec	0	0	0
Change from Baseline in Categories: Maximum Post-baseline [a, b]			
<-60 msec	0	0	0
≥-60 to <-30 msec	0	0	0
≥-30 to <0 msec	8 (7)	18 (8)	26 (11)
≥0 to <30 msec	85 (78)	160 (71)	161 (71)
≥30 to <60 msec	16 (15)	48 (21)	38 (17)
≥60 msec	0	0	2 (<1)

Abbreviations: QTc(F)=QT interval corrected for heart rate by Fridericia's formula; UMEC=umeclidinium bromide; VI=vilanterol

a. Baseline was the most recent recorded value before dosing on Day 1. For the majority of subjects, this was their predose value on Day 1.

b. Includes scheduled, unscheduled, and Early Withdrawal visits.

ECG Interpretations

Primary Efficacy Studies

The proportions of subjects in the Primary Efficacy Studies with an abnormal, clinically significant ECG interpretation were similar across treatment groups at baseline (Table 78). There were small differences in the proportion of subjects with reports of abnormal, clinically significant ECG interpretations between the individual components (UMEC or VI) and placebo and no additive effect with the UMEC/VI combination.

There was no individual post-baseline abnormality with an incidence in any UMEC/VI, UMEC, or VI treatment group ≥2% higher than placebo. There was one subject with polymorphic (sustained and non-sustained) ventricular tachycardia with UMEC/VI 125/25 mcg; this event was not seen at baseline. Atrial arrhythmias were reported at a low incidence and are discussed in Section 5.4.3.1.

Table 78 Summary of ECG Result Interpretations (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

	Number (%) of Subjects						
	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Baseline [a]							
n	555	842	832	418	629	1034	423
Normal	313 (56)	499 (59)	471 (57)	237 (57)	363 (58)	605 (59)	235 (56)
Abnormal – not clinically significant	158 (28)	255 (30)	255 (31)	137 (33)	188 (30)	310 (30)	142 (34)
Abnormal – clinically significant	84 (15)	88 (10)	105 (13)	44 (11)	77 (12)	115 (11)	45 (11)
Unable to evaluate	0	0	1 (<1)	0	1 (<1)	4 (<1)	1 (<1)
Any Time Post-baseline [b]							
n	555	842	832	417	629	1034	423
Normal	195 (35)	318 (38)	308 (37)	163 (39)	238 (38)	375 (36)	160 (38)
Abnormal – not clinically significant	237 (43)	363 (43)	346 (42)	178 (43)	279 (44)	437 (42)	180 (43)
Abnormal – clinically significant	123 (22)	161 (19)	178 (21)	76 (18)	112 (18)	222 (21)	83 (20)
Unable to evaluate	0	0	0	0	0	0	0

Abbreviations: ECG=electrocardiogram;; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

a. Baseline was the most recent recorded value before dosing on Day 1. For the majority of subjects, this was their predose value on Day 1.

b. Worst interpretation recorded at a scheduled, unscheduled, or Early Withdrawal visit made after the start of study treatment.

Long-term Safety Study

In study 359, the proportions of subjects with an abnormal, clinically significant ECG interpretation were similar across treatment groups at baseline and post-baseline (Table 79). There were no post-baseline ECG abnormalities of ventricular tachycardia. As in the Primary Efficacy Studies, atrial arrhythmias were reported at a low incidence and are discussed in Section 5.4.3.1.

Table 79 Summary of ECG Result Interpretations (Study 359)

	Number (%) of Subjects		
	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Baseline [a]			
n	109	226	227
Normal	66 (61)	133 (59)	141 (62)
Abnormal - not clinically significant	34 (31)	68 (30)	66 (29)
Abnormal - clinically significant	9 (8)	24 (11)	20 (9)
Unable to evaluate	0	1 (<1)	0
Any Time Post-baseline [b]			
n	109	226	227
Normal	32 (29)	71 (31)	64 (28)
Abnormal – not clinically significant	52 (48)	101 (45)	105 (46)
Abnormal – clinically significant	25 (23)	54 (24)	58 (26)
Unable to evaluate	0	0	0

Abbreviations: ECG=electrocardiogram; UMEC=umeclidinium bromide; VI=vilanterol

a. Baseline was the most recent recorded value before dosing on Day 1. For the majority of subjects, this was their predose value on Day 1.

b. Includes any ECG at any time post-baseline, including scheduled, unscheduled, and Early Withdrawal visits. Only worst case interpretation was counted for each subject.

5.4.4.2. 24-Hour Holter ECGs

Overall, a total of 1393 Holter ECGs were obtained from 394 subjects from a subset of the 2 placebo-controlled Primary Efficacy Studies and 2217 were obtained from 495 subjects in study 359.

In the placebo-controlled Primary Efficacy Studies, 24-hour Holter ECGs were obtained at Screening, Day 1, Day 84, and Day 168 in a subset of subjects. In study 359, 24-hour Holter measurements were obtained on all subjects at Screening and Days 91, 182, 273, and 364. Holter monitoring was not performed in the active-comparator Primary Efficacy Studies (studies 360 and 374).

The 24-hour Holter monitors (12-lead) were provided by an external vendor and data were electronically transmitted to an independent cardiologist for evaluation. The independent cardiologist, blinded to treatment assignment, was responsible for providing an interpretation of Holter findings.

Primary Efficacy Studies

There were no clinically meaningful or treatment-related effects on Holter ECG HRs, ventricular ectopics, or supraventricular ectopics in the Primary Efficacy Studies.

The proportions of subjects with an abnormal, clinically significant Holter ECG interpretation were similar at Screening (29% to 35% across the UMEC/VI, UMEC, and VI treatment groups compared with 36% for placebo) and post-baseline (45% to 56% in the UMEC/VI, UMEC, and

VI treatment groups compared with 60% for placebo) (Table 80). The change from Screening was reported as an unfavorable clinically significant change for 25% to 42% of subjects in the UMEC/VI, UMEC, and VI treatment groups compared with 39% for placebo. Atrial arrhythmias were reported at a low incidence and are discussed in Section 5.4.3.1. The incidence of Holter findings of ventricular tachycardia was similar in the active treatment groups compared with placebo (Table 81). None of these events were reported at baseline.

Table 80 Summary of Holter ECG Result Interpretations (DB2113361 and DB2113373 [TFH Population])

	Number (%) of Subjects					
	Placebo N=73	UMEC/VI 62.5/25 N=53	UMEC/VI 125/25 N=55	UMEC 62.5 N=54	UMEC 125 N=53	VI 25 N=108
Screening						
n	73	52	55	54	53	107
Normal	45 (62)	33 (63)	33 (60)	32 (59)	34 (64)	72 (67)
Abnormal – not clinically significant	1 (1)	1 (2)	3 (5)	2 (4)	2 (4)	5 (5)
Abnormal – clinically significant	26 (36)	15 (29)	19 (35)	18 (33)	15 (28)	26 (24)
Unable to evaluate	1 (1)	3 (6)	0	2 (4)	2 (4)	4 (4)
Any Time Post-baseline [a,b]						
n	72	53 [c]	55	54	53	107
Normal	27 (38)	25 (47)	27 (49)	24 (44)	23 (43)	49 (46)
Abnormal – not clinically significant	1 (1)	0	3 (5)	0	1 (2)	5 (5)
Abnormal –- clinically significant	43 (60)	28 (53)	25 (45)	30 (56)	29 (55)	52 (49)
Unable to evaluate	1 (1)	0	0	0	0	1 (<1)
Change from Screening to Any Time Post-baseline [a,b]						
n	72	53 [c]	55	54	53	107
Clinically significant change: favorable	3 (4)	4 (8)	2 (4)	3 (6)	4 (8)	5 (5)
No change or insignificant change	40 (56)	28 (53)	39 (71)	29 (54)	25 (47)	64 (60)
Clinically significant change: unfavorable	28 (39)	19 (36)	14 (25)	20 (37)	22 (42)	33 (31)
Unable to compare	1 (1)	2 (4)	0	2 (4)	2 (4)	5 (5)

Abbreviations: ECG=electrocardiogram; TFH=twenty-four hour; UMEC=umeclidinium bromide; VI=vilanterol

a. Includes scheduled and unscheduled Holters.
b. Represents any time post Screening.
c. One subject has Holter records during the treatment period for both the result interpretation (e.g., Normal, Abnormal) and the change in result (e.g., No change, Clinically significant change), but has no Holter data at the *scheduled* Screening visit. They did have an *unscheduled* Screening assessment, which is not summarized in this table but was used to determine the change interpretation for the on-treatment assessments for this subject.

Table 81 Selected Ventricular Arrhythmia Holter ECG Findings from All Subjects with Any Abnormal Clinically Significant Holter ECG Abnormality (Studies 361 and 373 [TFH Subset])

	Number (%) of Subjects					
	Placebo N=73	UMEC/VI 62.5/25 N=53	UMEC/VI 125/25 N=55	UMEC 62.5 N=54	UMEC 125 N=53	VI 25 N=108
Screening ventricular arrhythmias						
n	73	52	55	54	53	107
Non-sustained ventricular tachycardia (>100 bpm, 3-30 beats)	0	0	0	0	0	0
Sustained ventricular tachycardia (>100 bpm, >30 beats)	0	0	0	0	0	0
Post-randomization ventricular arrhythmias						
n	72	53	55	54	53	107
Non-sustained ventricular tachycardia (>100 bpm, 3-30 beats)	11 (15)	5 (9)	2 (4)	4 (7)	7 (13)	12 (11)
Sustained ventricular tachycardia (>100 bpm, >30 beats)	1 (1)	0	1 (2)	0	0	0

Abbreviations: ECG=electrocardiogram; TFH=twenty-four hour; UMEC=umeclidinium bromide; VI=vilanterol.

Long-term Safety Study

There were no clinically meaningful or treatment-related effects on Holter ECG HRs, ventricular ectopics, or supraventricular ectopics.

The proportions of subjects with an abnormal, clinically significant overall Holter ECG interpretation were similar in each treatment group at Screening (UMEC 125 mcg: 27%; UMEC/VI 125/25 mcg: 28%; placebo: 24%) and after randomization (UMEC 125 mcg: 55%; UMEC/VI 125/25 mcg: 55%; placebo: 52%) (Table 82). The change from Screening was reported as an unfavorable clinically significant change in similar percentages of subjects in each treatment group (UMEC 125 mcg: 43%; UMEC/VI 125/25 mcg: 42%; placebo: 43%). Atrial arrhythmias were reported at a low incidence and are discussed in Section 5.4.3.1.

Table 82 Summary of Holter ECG Result Interpretations (Study 359)

	Number (%) of Subjects		
	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Screening			
n	109	226	227
Normal	80 (73)	157 (69)	154 (68)
Abnormal – not clinically significant	3 (3)	6 (3)	10 (4)
Abnormal – clinically significant	26 (24)	63 (28)	62 (27)
Unable to evaluate	0	0	1 (<1)
Any Time Post-baseline [a]			
n	90	207	198
Normal	39 (43)	88 (43)	79 (40)
Abnormal – not clinically significant	4 (4)	3 (1)	8 (4)
Abnormal – clinically significant	47 (52)	114 (55)	109 (55)
Unable to evaluate	0	2 (<1)	2 (1)
Change From Screening to Any Time Post-baseline [a]			
n	90	207	198
Clinically significant change: favorable	3 (3)	4 (2)	6 (3)
No change or insignificant change	46 (51)	110 (53)	98 (49)
Clinically significant change: unfavorable	39 (43)	87 (42)	86 (43)
Unable to compare	2 (2)	6 (3)	8 (4)

Abbreviations: ECG=electrocardiogram; ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol

a. Includes scheduled and unscheduled Holters.

The incidence of Holter findings of ventricular tachycardia was similar in the active treatment groups compared with placebo (Table 73). None of these events were reported at baseline except for one subject treated with UMEC 125 mcg with a Holter finding of non-sustained ventricular tachycardia (>100bpm, 3-30 beats).

Table 83 Selected Ventricular Arrhythmia Holter ECG Findings from All Subjects with Any Abnormal Clinically Significant Holter ECG Abnormality (Study 359)

	Number (%) of Subjects		
	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Screening – ventricular arrhythmias			
n	109	226	227
Non-sustained ventricular tachycardia (>100 bpm, 3-30 beats)	0	0	1 (<1)
Sustained ventricular tachycardia (>100 bpm, >30 beats)	0	0	0
Post-randomization ventricular arrhythmias			
n	90	207	198
Non-sustained ventricular tachycardia (>100 bpm, 3-30 beats)	11 (12)	22 (11)	16 (8)
Sustained ventricular tachycardia (>100 bpm, >30 beats)	0	0	0

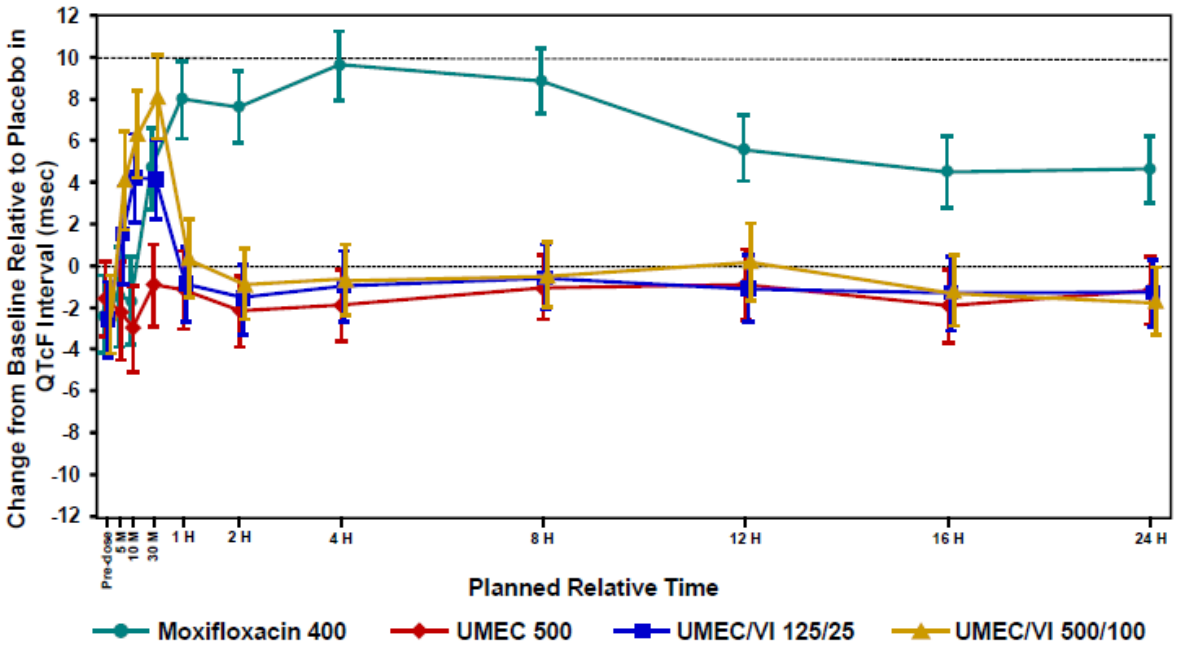
Abbreviations: ECG=electrocardiogram; TFH=twenty-four hour; UMEC=umeclidinium bromide; VI=vilanterol.

5.4.4.3. Thorough QT Study in Healthy Volunteers

In accordance with ICH E14 guidance [ICH E14], the effect of UMEC/VI on the QT interval was evaluated in a placebo and moxifloxacin controlled thorough QT study. Following once-daily administration of pre-dispensed doses of UMEC/VI 125/25 mcg for 10 days in healthy volunteers, no clinically relevant effect on prolongation of QTc(F) interval was observed.

Adjusted mean change from baseline compared with placebo is displayed over time in Figure 36. Repeat-dose UMEC/VI 125/25 mcg for 10 days showed no evidence of an effect on QTc(F) compared with placebo as the LS mean treatment difference did not exceed 5 milliseconds and the upper bound of the 90% CI for the estimated treatment difference did not exceed 10 milliseconds at any time point during 0 to 24 hours after dosing. The estimated treatment difference from placebo in QTc(F) was negative at all time points post last dose on Day 10, and the upper limit of the 90% CI for the estimated mean treatment difference was less than 10 milliseconds, indicating a lack of UMEC 500 mcg effect on QTc(F) compared with placebo. At a dose representing a 4 times higher UMEC/VI dose studied in Phase 3 clinical trials (500/100 mcg for 10 days), there was evidence of an increase in QTc(F) during the first hour after dosing. The largest mean time-matched difference from placebo was 8.2 milliseconds (90% CI: 6.2, 10.2) at 30 minutes after dosing. This was the only time point where the upper limit of the 90% CI exceeded 10 milliseconds and QTc(F) differences from placebo declined rapidly after this.

Figure 36 Differences from Placebo (90% CI) in Adjusted Mean Change from Baseline in QTc(F) Over Time on Day 10 (Study 635)



Abbreviations: CI=confidence interval: Moxi=moxifloxacin; QTcF= QT interval corrected for heart rate by Fridericia's formula; UMEC=umeclidinium bromide; VI=vilanterol.

5.4.5. Vital Signs

No clinically meaningful effects on vital signs (pulse rate, systolic blood pressure, diastolic blood pressure) were observed for either UMEC/VI or the individual components compared with placebo in the Primary Efficacy Studies or study 359. Maximum or minimum post-baseline mean changes from baseline in vital signs were small and similar across all treatment groups in both the Primary Efficacy Studies (Table 84) and study 359 (Table 85).

Table 84 Maximum or Minimum Post-baseline Change from Baseline in Vital Signs (Integrated Primary Efficacy Studies 361, 373, 360, and 374)

	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Maximum Post-baseline [a] Change from Baseline in Systolic BP (mmHg)							
n	555	842	832	418	629	1034	423
Mean (SD)	13.2 (11.80)	13.4 (11.71)	12.8 (11.83)	13.2 (12.86)	14.0 (12.82)	13.0 (12.24)	12.5 (11.64)
Minimum Post-baseline [a] Change from Baseline in Diastolic BP (mmHg)							
n	555	842	832	418	629	1034	423
Mean (SD)	-9.5 (8.21)	-9.1 (8.16)	-9.2 (7.77)	-9.2 (7.97)	-9.7 (8.33)	-9.4 (8.10)	-8.9 (7.58)
Maximum Post-baseline [a] Change from Baseline in Pulse Rate (beats per minute)							
n	555	842	832	418	629	1034	423
Mean (SD)	9.9 (9.22)	9.3 (8.47)	9.8 (9.07)	10.1 (9.21)	9.9 (9.38)	9.6 (8.88)	9.9 (8.71)

Abbreviations: BP=blood pressure; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
a. Includes scheduled, unscheduled, and Ealry Wirhdrawal visits.

Table 85 Maximum or Minimum Post-baseline Change from Baseline in Vital Signs (Study 359)

	Placebo N=109	UMEC/VI 125/25 mcg N=226	UMEC 125 mcg N=227
Maximum Post-baseline [a] Change from Baseline in Systolic BP (mmHg)			
n	109	226	227
Mean (SD)	14.5 (15.28)	13.5 (13.02)	14.0 (14.05)
Minimum Post-baseline [a] Change from Baseline in Diastolic BP (mmHg)			
n	109	226	227
Mean (SD)	-11.0 (8.87)	-10.8 (8.89)	-9.5 (7.86)
Maximum Post-baseline[a] Change from Baseline in Pulse Rate (beats per minute)			
n	109	226	227
Mean (SD)	9.1 (9.30)	9.0 (9.04)	9.8 (10.16)

Abbreviations: BP=blood pressure; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
a. Includes scheduled, unscheduled, and Ealry Wirhdrawal visits.

5.5. Clinical Laboratory Evaluations

No liver concerns were identified with UMEC/VI, UMEC or VI treatments in the Primary Efficacy Studies or study 359. The few reports of liver abnormalities were generally transient or confounded by concurrent medical conditions or concomitant medications.

Based on the review of shifts with respect to the normal reference range for hematology and clinical chemistry analytes, no trends were observed suggesting an effect of UMEC/VI or its individual components (UMEC and VI) on the occurrence of laboratory values outside the normal range in either the Primary Efficacy Studies or study 359. There was no indication from the routine laboratory evaluations of a clinically remarkable treatment-related or dose-related effect on glucose or potassium.

5.6. Clinical Safety Conclusions

UMEC/VI was well tolerated with a similar rate of AEs across all treatment groups including placebo and no significant safety concerns. No difference in the safety profile was observed between the 2 doses of UMEC/VI. There was no evidence of additive adverse effects for the combination of UMEC/VI over the individual components.

The incidence of pharmacologic effects such as dry mouth and tremor was low and the incidence with UMEC/VI was similar to placebo. Atrial arrhythmias, a likely pharmacology-related event, were observed at a low incidence with UMEC/VI treatment groups that was slightly higher than with placebo.

Active treatment groups showed no evidence of increased MACE compared to placebo. Non-fatal myocardial infarction was also reported at a low incidence across all treatment groups. Small imbalances in exposure-adjusted frequency between UMEC/VI treatment groups when compared with placebo were observed. There was no dose relationship or additive effect from the combination. Whether this represents a true effect on myocardial infarction is difficult to determine due to the small number of events.

The data indicate that UMEC/VI 62.5/25 mcg can be safely administered to patients with COPD.

6. RISK MANAGEMENT PLAN

A global Risk Management Plan was submitted as part of the NDA, and will be routinely used to monitor UMEC/VI safety-related information.

The following are considered important potential risks with UMEC/VI combination:

- Asthma-related Intubations and Deaths
- Cardiac Disorders

6.1. Asthma-related Intubations and Deaths

Asthma-related intubations and deaths that may be associated with LABA monotherapy use in asthmatics are included as a potential risk. Risk minimization activities in the proposed ANORO

ELLIPTA Prescribing Information include the class labeling Boxed Warning regarding the risk of asthma-related death observed in a placebo-controlled trial with another LABA (salmeterol).

Routine post-marketing pharmacovigilance activities to monitor the further will include:

- Evaluation of individual case safety reports (ICSRs) in the safety database.
- Aggregate review of spontaneous and clinical trial case data from the safety database.
- Off- label use, particularly in asthmatics (without concurrent COPD) will be monitored through active pharmacovigilance and studied via a drug utilization study.

6.2. Cardiac Disorders

Both the LAMA and LABA classes of drugs have been associated with some increased risk of CV events. Clinical experience to date with UMEC/VI has not shown any robust associations with cardiac events, particularly no associations were observed with cardiac events linked to significant or serious consequences. A low number of atrial arrhythmias were reported (based on AEs, 12-lead ECGs, or Holter ECGs), of which some occurred with a higher incidence in active treatment groups compared to placebo. There was no additive effect with the combination over individual components. Few of these findings were reported as SAEs and none were fatal. Risk minimization activities in the "Warnings and Precautions" section of the proposed ANORO ELLIPTA Prescribing Information include class labeling that UMEC/VI should be used with caution in patients with CV disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Routine post-marketing pharmacovigilance activities to monitor the risk further will include:

- Evaluation of ICSRs in the safety database.
- Aggregate review of spontaneous and clinical trial case data from the safety database, using disproportionality analysis.
- Signal detection utilizing large population-based observational databases.
- Monthly review of published literature.
- In-period scientific evaluations to be included in PSUR or equivalent report.

The proposed ANORO ELLIPTA US Prescribing Information will include adverse reactions observed during clinical studies. Additionally, class warnings and precautions that may not have been observed during clinical studies will be included.

6.3. Other Considerations and Monitoring

While no anticholinergic effects relating to ocular effects or relating to urinary retention were noted with UMEC/VI in COPD patients, similar to the currently available LAMAs for treatment of COPD, the "Warnings and Precautions" section of the proposed ANORO ELLIPTA US Prescribing Information includes a warning regarding use in patients with narrow-angle glaucoma and with urinary retention.

Additional information will be collected on reported events of pregnancy through active pharmacovigilance and in ongoing clinical studies. Off label use, particularly in asthmatics (without concurrent COPD) including pediatric use will be monitored through active pharmacovigilance and studied via a drug utilization study.

7. BENEFIT AND RISK CONCLUSIONS

7.1. Therapeutic Justification

Long-acting bronchodilators are recommended by guidelines for treatment of COPD to improve airflow obstruction and reduce symptoms. By targeting 2 different pharmacologic mechanisms, a LAMA/LABA combination product could potentially optimize bronchodilator therapy of COPD over bronchodilator monotherapy while avoiding the risk of side effects associated with increasing the dose of a single bronchodilator [Cazzola, 2010]. Furthermore in a disease where polypharmacy is widespread, a once-daily LAMA/LABA combination in a single inhaler has the potential to not only optimize bronchodilator therapy but also to improve patient adherence and convenience and, as a result, improve overall COPD disease management. UMEC/VI, a once-daily LAMA/LABA combination in a single inhaler, offers a new therapeutic option for the first line maintenance treatment of COPD.

7.2. Benefit/Risk

The UMEC/VI development program has demonstrated that UMEC/VI 62.5/25 mcg provides clinically relevant efficacy, as defined by measures of lung function over 24 weeks of treatment, as compared with placebo, the individual monotherapies and tiotropium in a broad range of subjects with COPD. The contribution of each component of UMEC/VI 62.5/25 mcg is supported by the superiority of the UMEC/VI combination over UMEC 62.5 mcg or VI 25 mcg as monotherapy in measures of lung function. Though neither UMEC 62.5 mcg nor VI 25 mcg is currently approved, both were shown to be efficacious compared with placebo and to have a duration of action that supports once-daily administration. In addition to efficacy on lung function, UMEC/VI 62.5/25 mcg reduced rescue medication use, improved health-related quality of life (based on SGRQ), and improved symptoms of dyspnea as measured by TDI scores compared with placebo thereby providing additional evidence of beneficial effect.

UMEC/VI was well tolerated with a similar rate of AEs across all treatment groups including placebo and no significant safety concerns. No difference in the safety profile was observed between the 2 doses of UMEC/VI. Potential pharmacology-related effects such as atrial arrhythmias were observed at a low incidence with UMEC/VI treatment groups that was slightly higher than with placebo. Non-fatal myocardial infarction was also reported at a low incidence across all treatment groups. Small imbalances in exposure-adjusted frequency of non-fatal myocardial infarction between UMEC/VI treatment groups when compared with placebo were observed. There was no dose relationship or additive effect from the combination. Whether this represents a true effect on myocardial infarction is difficult to determine due to the small number of events.

The benefits of UMEC/VI 62.5/25 include improved pulmonary function, symptoms, and health-related quality of life. The overall safety profile shows a low incidence of

pharmacologically predicted AEs and the data demonstrate no evidence of an increased risk with UMEC/VI over the individual components, supporting the overall conclusion of a positive benefit-risk balance for UMEC/VI 62.5/25 as a maintenance bronchodilator treatment for COPD.

8. OVERALL CONCLUSION

In conclusion, ANORO ELLIPTA is a novel once-daily LAMA/LABA combination product UMEC/VI 62.5/25 mcg will provide a new treatment to optimize maintenance bronchodilator therapy over LAMA or LABA monotherapy with sustained efficacy over 24 hours. The safety and tolerability profile of UMEC/VI has been well characterized with no significant safety findings. UMEC/VI 62.5/25 mcg will be a safe and effective treatment available for patients who suffer from COPD.

9. REFERENCES

Aaron SD, Vandemheen KL, Fergusson D, et al, for the Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Tiotropium in combination with placebo, salmeterol, or fluticasone–salmeterol for treatment of chronic obstructive pulmonary disease. A randomized trial. *Ann Intern Med*. 2007;146:545-55.

Anthonisen NR, Connett JE, Enright PL, et al. for the Lung Health Study Research Group. Hospitalizations and mortality in the lung health study. *Am J Respir Crit Care Med.* 2002;166:333-339.

Cazzola M, Noschese P, Salzillo A, et al. Bronchodilator response to formoterol after regular tiotropium or to tiotropium after regular formoterol in COPD patients. *Respir Med.* 2005 May;99(5):524-8.

Cazzola M, Centanni S, Santus P, et al. The functional impact of adding salmeterol and tiotropium in patients with stable COPD. *Respir Med.* 2004 Dec;98(12):1214-21.

Cazzola M, Molimard M. The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. *Pulm Pharmacol Ther*. 2010;23(4):257-67.

Center for Drug Evaluation and Research (CDER), Medical Reviews, aclidinium bromide, 25 May 2012, http://www.accessdata.fda.gov/drugsatfdadocs/nda/2012/202450Orig1s000MedR.pdf Accessed 06 Dec 2012.

Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J.* 2004;23:932-946.

Chapman KR, Mannino DM, Soriano JB, et al. Epidemiology and costs of Chronic Obstructive Pulmonary Disease. *Eur Respir J*. 2006;27:188-207.

Curkendall SM, DeLuise C, Jones JK, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol.*2006;16:63-70.

FDA Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Federal Register. 2009; 71:5862.

GOLD Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013. Available from: http://www.goldcopd.org/.

Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Resp Crit Care Med*. 1999;159:179-187.

Hankinson JL, Kawut SM, Shahar E, et al. Performance of American Thoracic Society - Recommended spirometry reference values in a multiethnic sample of adults: The Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. *Chest*. 2010;137:138-45.

Howard K, Berry P, Petrillo J, et al. Shortness of Breath with Daily Activities Questionnaire (SOBDA). *Values in Health.* 2012;15:1042-1050.

International Conference on Harmonisation (ICH E1). ICH Harmonized Tripartite Guideline: Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-life Threatening Conditions E1 (Step 4). Web site: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf. Accessed 22 May, 2013.

International Conference on Harmonisation (ICH E14). The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf. Accessed 19 July, 2013.

Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis*. 1992;145:1321-7.

Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD*. 2005;2:75-9.

Kosacz NM. Chronic Obstructive Pulmonary Disease Among Adults. MMWR. 2012 Nov; 61(46):938-943.

Lopez AD, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J*. 2006;27:397-412.

Mahler DA, Witek TJ Jr. The MCID of the transition dyspnea index is a total score of one unit. *COPD*. 2005 Mar;2(1):99-103.

Murphy SL, Xu JQ, Kochanek KD. Deaths: Preliminary data for 2010. National vital statistics reports; vol 60 no 4. Hyattsville, MD: National Center for Health Statistics. 2012.

Pepin V, Saey D, Whittom F, et al. Walking versus cycling. Sensitivity to bronchodilation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;172:1517-1522.

Pepin V, Laviolette L, Brouillard C, et al. Significance of changes in endurance shuttle walking performance. *Thorax.* 2011;66:115-20.

Tashkin DA, Littner M, Andrews CP, et al. Concomitant treatment with nebulized formoterol and tiotropium in subjects with COPD: A placebo-controlled trial. *Respir Med. 2008*;102:479–87.

Tashkin DP, Pearle J, Iezzoni D, Varghese ST. Formoterol and tiotropium compared with tiotropium alone for treatment of COPD. *COPD.* 2009 Feb;6(1):17-25.

Tashkin DB, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. *Respir Res.* 2013;May 8;14-49.

Van Noord JA, Aumann JL, Janssens E, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur Respir J*. 2005 Aug;26(2):214-22.

Van Noord JA, Aumann JL, Janssens E, et al. Effect of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. *Chest*. 2006;129(3):509-17.

Witek TJ Jr, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *Eur Respir J*. 2003 Feb;21(2):267-72.

10. APPENDICES

10.1. Nonclinical Pharmacology and Toxicology

The pharmacological, PK and toxicological effects of UMEC or VI when administered alone have been well characterized in a comprehensive range of nonclinical studies to support their long-term clinical use. Nonclinical safety assessment packages for UMEC and VI as single agents include safety pharmacology, repeat-dose general toxicology, genetic toxicology, carcinogenicity and reproductive toxicology studies. Combination toxicology bridging studies applicable to 'late stage' entities, have also been performed. The human responses to LAMAs and LABAs have been comprehensively studied and, based on this experience and on the data derived from animal studies, appropriate monitoring for potential adverse effects in clinical studies was included in the UMEC/VI COPD Clinical Development Program.

The toxicology findings from UMEC and VI alone and in combination were generally associated with their primary pharmacology and/or local irritancy and there is no indication that the findings raise any significant safety concerns for the use in humans of UMEC and VI in the proposed commercial inhaled drug product. This conclusion is supported by the clinical safety assessments which indicate that UMEC and VI drug product, at the proposed commercial once-daily UMEC/VI dose of 62.5/25 mcg/day and also at the higher dose of 125/25 mcg/day, was well tolerated in adult subjects with COPD. UMEC/VI is designated as Pregnancy Category C.

10.2. Overview of Clinical Pharmacology and Pharmacokinetics

A total of 40 clinical studies have been conducted evaluating the clinical pharmacology of UMEC/VI and the UMEC and VI monotherapies. Studies conducted with UMEC alone or VI alone included administration by the inhaled (IH), intravenous (IV), and oral (PO) routes. These studies were conducted predominantly in healthy subjects but also included subjects with COPD, subjects with moderate hepatic impairment, and subjects with severe renal impairment.

In certain instances, PK and PD data for VI is taken from studies which utilized VI in combination with FF. The rationale to support the use of PK and PD data from these studies is in part due to the fact that no differences in VI pharmacokinetics are observed when VI is administered alone or in combination with FF.

When UMEC and VI were administered in combination by the inhaled route, the PK parameters for each component were similar to those observed when each was administered separately.

Metabolism and PK properties of UMEC and VI are summarized in Table 86.

Table 86 Metabolism and PK Properties of UMEC and VI

Parameter		UMEC	VI
Absorption	t_{max}	5-15 min [a]	5-15 min[a]
	Inhaled Bioavailability (IH)	13%[b]	27% [d]
	Steady State	7-10 days [c]	6 days [c]
	Oral absorption	~5% (based on radiolabeled metabolites, no parent drug following oral)	~50% of radiolabel (<0.5% parent) indicative of high first pass metabolism
Distribution	Mean vol. distribution	86 L[e]	165 L
	Plasma Protein Binding	89% [f]	94%
Metabolism and Elimination (Disposition)	Primary metabolic route	Oxidative (hydroxylation, *O*-dealkylation) followed by conjugation (glucuronide / others)	*O*-dealkylation
	Elimination/disposition pathways	Biliary secretion of unchanged drug and metabolites following IV administration (highest possible load) resulting in 73% and 27% of recovered radioactivity in feces and in urine, respectively.	Metabolism - metabolites excreted both in urine (70%) and feces (30%) of recovered radioactivity.
	% excreted in urine following inhaled dosing	~1-2% following single dose [b] ~3-4% following repeat doses [c]	~1-2% following single dose [b] Following repeat doses [c] NA
	Plasma Clearance	151 L/h [e]	108 L/h [e]
	Elimination $t_{1/2}$ (IH)	~ 19h [e, g]	~ 11h [e, g]
	Renal Clearance	~ 6-20 L/h [e] (elimination by glomerular filtration + tubular secretion)	NA
Drug-drug Interaction		UMEC is a substrate for CYP2D6 and the P-gp transporter. No clinically significant increase in exposure was observed in CYP2D6 poor metabolizers. In healthy subjects, co-administration of UMEC at steady state with the moderate P-gp inhibitor verapamil resulted in 1.4-fold higher systemic exposure (AUC) with no effect on C_{max}.	VI is a substrate for CYP3A4 and the P-gp transporter. Co-administration of repeat oral dose ketoconazole (strong CYP3A4 inhibitor) (400 mg) and single dose inhaled VI (25 mcg) resulted in on average a 1.9-fold increase in VI systemic exposure as measured by $AUC_{(0-t)}$ and no change in VI C_{max}. In healthy subjects, co-administration of VI (as UMEC/VI) at steady state with the moderate CYP3A4 inhibitor and moderate P-gp inhibitor verapamil resulted in no effect on systemic exposure (AUC or C_{max})
Intrinsic Factors	Renal Impairment	No dose adjustment is warranted in patients with severe renal impairment.	
	Hepatic Impairment	No dose adjustment is warranted in patients with mild to moderate hepatic impairment. UMEC was not investigated in subjects with severe hepatic impairment.	No dose adjustment is warranted in patients with mild to moderate hepatic impairment.
	Population PK	UMEC and VI utilizing data from 2 controlled clinical studies that included	

Parameter		UMEC	VI
	Analysis (age, gender, weight, CLcr)	Subjects with COPD (UMEC n=1635; VI n=1637) who received treatment with inhaled UMEC/VI. No dose adjustment is warranted based on the effect of age (40 to 93 years), gender (69% male), or weight (34 to 161 kg) or creatinine clearance. There was also no evidence of a clinically significant effect of ethnicity on systemic exposure to either UMEC or VI.	

Abbreviations: AUC=area under the curve; Clcr=creatinine clearance; Cmax=maximum observed concentration; COPD=chronic obstructive pulmonary disease; FF=fluticasone furoate; IH=inhaled; IV=intravenous; $t_{1/2}$=terminal phase half-life; tmax= time of occurrence of C_{max}; NA=not applicable; P-gp= P-glycoprotein; PK=pharmacokinetics; UMEC=umeclidinium; VI=vilanterol

a. Following single- and repeat-dose
b. Single dose
c. Repeat dosing
d. Following 4 inhalations of FF/VI 200/25 mcg
e. Geometric Mean
f. In vitro human plasma protein binding
g. Following repeat dosing with UMEC/VI 125/25 mcg (Study 635)

10.2.1. Umeclidinium

10.2.1.1. Absorption and Distribution

Following inhaled administration of UMEC, maximum concentration (C_{max}) occurred at 5–15 minutes following single and repeat dose. The absolute bioavailability of a single dose of inhaled UMEC in healthy subjects was on average 13% of the dose. Following repeat dosing with inhaled UMEC, steady-state was achieved within 7 to 10 days with mean accumulation ratio of 1.5 to 2.0 fold.

Following IV administration, the geometric mean volume of distribution of UMEC was 86L, suggestive of significant tissue distribution. In vitro plasma protein binding in human plasma was on average 89%.

10.2.1.2. Metabolism and Elimination

The primary metabolic routes for UMEC are oxidative (hydroxylation, O-dealkylation) followed by conjugation (e.g., glucuronidation), resulting in a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Systemic exposure to the metabolites is low. Following oral administration total mean recovery of radioactivity in the feces and urine at 168h was 92% and <1% of the administered oral UMEC dose, respectively, confirming low gut absorption. Most of the excreted radioactivity (on average 85% in feces and 0.72% in urine) was eliminated within the first 48h.

10.2.1.3. Drug-Drug Interaction

Umeclidinium is a substrate for P-glycoprotein (P-gp) transporter. In healthy volunteers, concomitant administration of UMEC at steady-state with the P-gp inhibitor verapamil resulted in 1.4-fold higher systemic exposure (area under the curve [AUC]) and no effect on C_{max}.

10.2.2. Vilanterol

10.2.2.1. Absorption and Distribution

Following inhaled administration of VI, C_{max} occurred at 5 to 15 minutes followed by rapid clearance and elimination. The pharmacokinetics of VI are independent of co-administration with FF. Absolute bioavailability of VI when administered by 4 inhalations of the FF 200 mcg/VI 25 mcg combination (total dose FF 800 mcg /VI 100 mcg) was 27%.

Following IV administration to healthy subjects, the mean volume of distribution at steady state was 165 L. Binding of VI to human plasma proteins was 4%.

10.2.2.2. Metabolism and Elimination

Vilanterol is metabolized, principally via CYP3A4, by O-dealkylation to a range of metabolites with significantly reduced β1- and β2-agonist activity. Plasma metabolic profiles following oral administration of VI in a human radiolabel study were consistent with high first pass metabolism.

10.2.2.3. Drug-Drug Interaction

Vilanterol is primarily metabolized by CYP3A4. Co-administration of repeat oral dose ketoconazole (400 mg), a strong CYP3A4 inhibitor, and single dose inhaled VI 25 mcg resulted in on average a 1.9-fold increase in systemic exposure as measured by AUC(0–t) and no change in the VI C_{max}. Vilanterol is a substrate for the P-gp transporter. In healthy volunteers, concomitant administration of VI at steady-state with the P-gp inhibitor verapamil resulted in no effect on AUC or C_{max}.

10.2.3. Umeclidinium and Vilanterol in Special Populations (Intrinsic Factors)

10.2.3.1. Baseline and Demographic PK Covariates

A population PK analysis was performed for UMEC and VI utilizing data from 2 controlled clinical trials that included 1635 COPD patients who received treatment with inhaled UMEC/VI. The population analysis showed that no dose adjustment is warranted based on the effect of age (40 to 93 years), gender (69% male), ICS use (48%), or weight (34 to 161 kg). There was also no evidence of a clinically significant effect of ethnicity on systemic exposure to either UMEC or VI.

10.2.3.2. Cytochrome P450 CYP2D6 Poor Metabolizers

Umeclidinium is metabolized by the enzyme CYP2D6. No clinically significant increase in exposure was observed in a healthy population deficient in CYP2D6 metabolism.

10.2.3.3. Hepatic impairment

Subjects with moderate hepatic impairment (Child-Pugh score 7-9) showed no evidence of an increase in systemic exposure to either UMEC or VI (C_{max} and AUC), and no evidence of altered

protein binding between subjects with moderate hepatic impairment and healthy volunteers. UMEC/VI has not been evaluated in subjects with severe hepatic impairment.

10.2.3.4. Renal impairment

Subjects with severe renal impairment (creatinine clearance < 30mL/min) showed no evidence of an increase in systemic exposure to either UMEC or VI (C_{max} and AUC), and no evidence of altered protein binding between subjects with severe renal impairment and healthy volunteers.

10.2.4. Conclusions from Clinical Pharmacology and Pharmacokinetic Studies

- UMEC/VI pharmacokinetics is consistent with an inhaled medication with limited systemic exposure and rapid clearance.
- No dose adjustment for renal or hepatic impairment, age, gender, weight, ethnicity, or ICS use is warranted.

10.3. Statistical Methods

10.3.1. Statistical Testing Hierarchies

The closed testing hierarchies employed to control multiplicity for each Primary Efficacy Study are listed below. Tests were performed in the order listed. According to the strict terms of the hierarchy, each test was required to achieve statistical significance in order to draw inference from subsequent comparisons.

10.3.1.1. Study 361

- Trough FEV_1 on Day 169 for UMEC/VI 125/25 mcg vs. placebo
- Trough FEV_1 on Day 169 for UMEC 125 mcg vs. placebo
- Trough FEV_1 on Day 169 for VI 25 mcg vs. placebo
- Trough FEV_1 on Day 169 for UMEC/VI 125/25 mcg vs. VI 25 mcg
- Trough FEV_1 on Day 169 for UMEC/VI 125/25 mcg vs. UMEC 125 mcg
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 125/25 mcg vs. placebo
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC 125 mcg vs. placebo
- 0 to 6 hour weighted mean FEV_1 on Day 168 for VI 25 mcg vs. placebo
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 125/25 mcg vs. VI 25 mcg
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 125/25 mcg vs. UMEC 125 mcg

10.3.1.2. Study 373

- Trough FEV_1 on Day 169 for UMEC/VI 62.5/25 mcg vs. placebo
- Trough FEV_1 on Day 169 for UMEC 62.5 mcg vs. placebo

- Trough FEV_1 on Day 169 for VI 25 mcg vs. placebo
- Trough FEV_1 on Day 169 for UMEC/VI 62.5/25 mcg vs. VI 25 mcg
- Trough FEV_1 on Day 169 for UMEC/VI 62.5/25 mcg vs. UMEC 62.5 mcg
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 62.5/25 mcg vs. placebo
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC 62.5 mcg vs. placebo
- 0 to 6 hour weighted mean FEV_1 on Day 168 for VI 25 mcg vs. placebo
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 62.5/25 mcg vs. VI 25 mcg
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 62.5/25 mcg vs. UMEC 62.5 mcg

10.3.1.3. Study 360

- Trough FEV_1 on Day 169 for UMEC/VI 125/25 mcg vs. tiotropium
- Trough FEV_1 on Day 169 UMEC/VI 125/25 mcg vs. VI 25 mcg
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 125/25 mcg vs. tiotropium
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 125/25 mcg vs. VI 25 mcg
- Trough FEV_1 on Day 169 for UMEC/VI 62.5/25 mcg vs. tiotropium
- Trough FEV_1 on Day 169 for UMEC/VI 62.5/25 mcg vs. VI 25 mcg
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 62.5/25 mcg vs. tiotropium
- 0 to 6 hour weighted mean FEV_1on Day 168 for UMEC/VI 62.5/25 mcg vs. VI 25 mcg

10.3.1.4. Study 374

- Trough FEV_1 on Day 169 for UMEC/VI 125/25 mcg vs. tiotropium
- Trough FEV_1 on Day 169 UMEC/VI 125/25 mcg vs. UMEC 125 mcg
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 125/25 mcg vs. tiotropium
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 125/25 mcg vs. UMEC 125 mcg
- Trough FEV_1 on Day 169 for UMEC/VI 62.5/25 mcg vs. tiotropium
- Trough FEV_1 on Day 169 for UMEC/VI 62.5/25 mcg vs. UMEC 125 mcg
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 62.5/25 mcg vs. tiotropium
- 0 to 6 hour weighted mean FEV_1 on Day 168 for UMEC/VI 62.5/25 mcg vs. UMEC 125 mcg

10.3.2. Missing Data

In the Primary Efficacy Studies, not all subjects completed all scheduled efficacy assessments, mainly due to withdrawal from the study. The methods used to investigate the impact of missing data on conclusions drawn from efficacy analyses are described below.

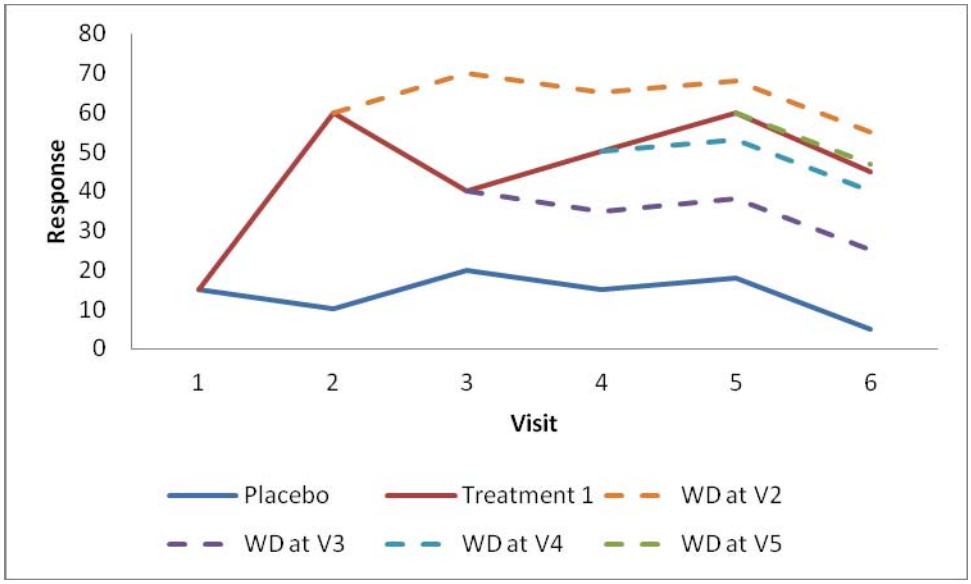
For the primary endpoint of trough FEV_1 on Day 169, the primary analysis was a MMRM analysis, which included all non-missing scheduled trough FEV_1 values. Missing data were not directly imputed in this analysis; however, all non-missing data for a subject were used within the analysis to estimate the treatment effect for trough FEV_1 on Day 169.

Sensitivity analyses using MI methods were conducted. Within each treatment group, a Bayesian multivariate normal model for the data (including the same covariates as for the primary MMRM analysis) was fitted using a Markov Chain Monte Carlo approach, and quasi-independent samples were drawn from the posterior distributions for the parameters of the multivariate normal distribution. Within treatment groups, the imputations were drawn separately for groups of subjects who withdrew at each visit. Imputations were based upon assumptions for the patterns of means post withdrawal, as described below, and were also conditioned on observations and covariate values for the individual subject observed prior to withdrawal.

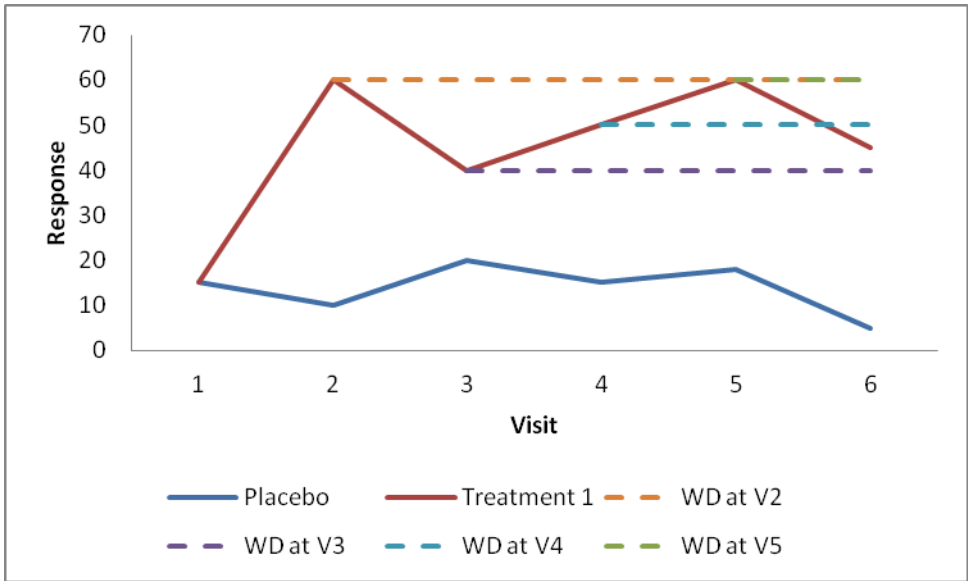
Four pre-planned MI methods were used:

1. Missing at random (MAR): Following withdrawal, the overall mean for withdrawn subjects will be the same as for subjects who remain on that treatment. Imputation is based on means and variance-covariances from subjects in the same treatment group as the withdrawn subject and is comparable to MMRM.

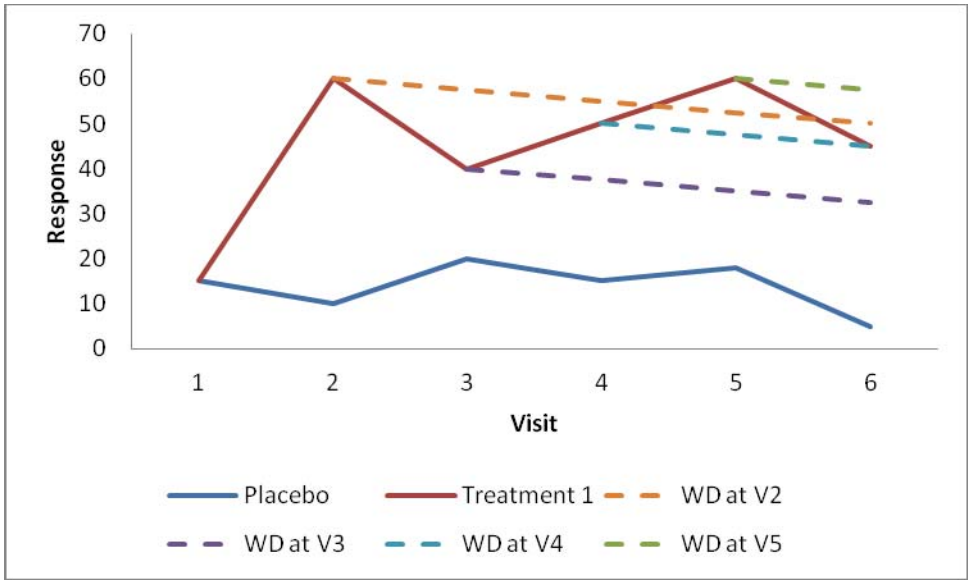
2. Copy difference from control (CDC): Following withdrawal, the overall mean for withdrawn subjects follows the same trend over time as that in the reference treatment group, but any benefit obtained from treatment prior to withdrawal is maintained.



3. Last Mean Carried Forward Assuming 0 mL/year Decline (LMCF0): Following withdrawal, the last observed mean is effectively carried forward.

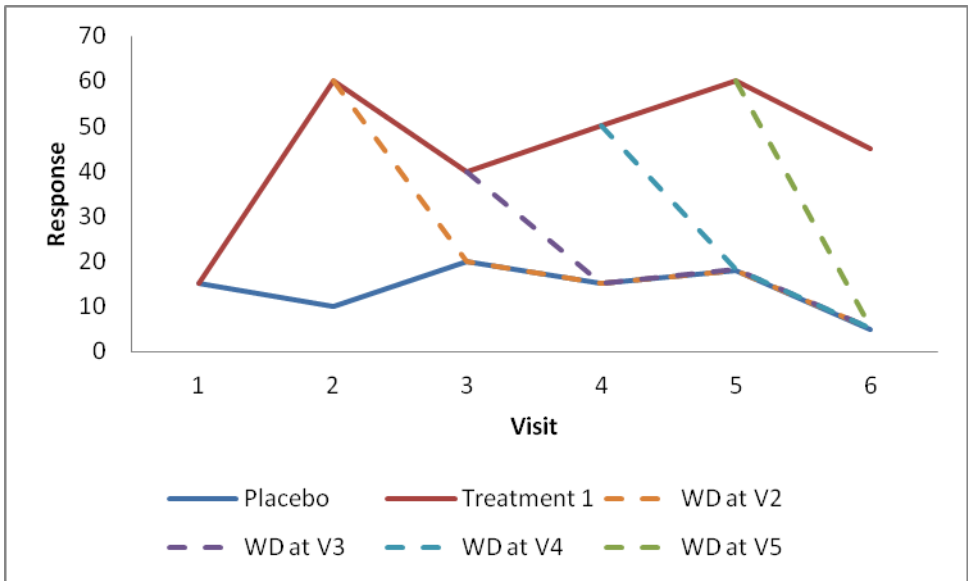


4. Last Mean Carried Forward Assuming 25 mL/year Decline (LMCF25): Following withdrawal, a constant rate of decline of 25 mL/year from the last observed mean is assumed.



Following FDA's request to explore imputation of missing data in active treatment groups using data from the reference treatment group, a further 2 MI methods were also used:

1. Jump to Reference (J2R): Following withdrawal, the overall mean for withdrawn subjects is assumed to be that in the reference group. This is the most extreme method, as the residuals from the mean in the active treatment group prior to withdrawal will be applied to the mean in the reference treatment group following withdrawal.



2. Copy Reference (CR): The overall mean for withdrawn subjects is assumed to be that in the reference treatment group, both before and after withdrawal. Any effect of treatment prior to withdrawal induces positive residuals which potentially feed through into the imputed values after withdrawal. This method is similar to "placebo mean" imputation.

In all these methods, the reference treatment group was placebo for the placebo-controlled studies and tiotropium for the active-comparator studies.

Similar MI sensitivity analyses were conducted for the secondary endpoint of 0 to 6 hour weighted mean FEV_1, and other efficacy endpoints of TDI and SOBDA. Following FDA request, these sensitivity analyses were also conducted for SGRQ.

10.4. Tabulation of Studies in All COPD Studies Grouping

A tabulation of studies in the All COPD Studies Grouping is provided in Table 87.

Table 87 All COPD Studies: Clinical Studies in COPD Subjects with Treatment Periods of at Least 4 Weeks and a Relevant Treatment Group

Study Identifier	Study Objective(s)	Study Design	Key Enrollment Criteria	Once-Daily Treatment (mcg) (IH) Treatment Duration	Total Number of Subjects Randomized/ Completed
Primary Efficacy Studies					
361	Evaluate efficacy and safety over 24 weeks	R, DB, PG, PC	• COPD subjects ≥40 years • post-bronchodilator FEV_1 ≤70% predicted and FEV_1/FVC <0.70 • mMRC dyspnea score ≥2	UMEC/VI 125/25 UMEC 125 VI 25 Placebo 24 weeks	Total:1489 403/325 407/312 404/298 275/183
373	Evaluate efficacy and safety over 24 weeks	R, DB, PG, PC	• COPD subjects ≥40 years • post-bronchodilator FEV_1 ≤70% predicted and FEV_1/FVC <0.70 • mMRC dyspnea score ≥2	UMEC/VI 62.5/25 UMEC 62.5 VI 25 Placebo 24 weeks	Total: 1532 413/332 418/324 421/318 280/204
360	Evaluate efficacy and safety over 24 weeks	R, DB, PG, AC	• COPD subjects ≥40 years • post-bronchodilator FEV_1 ≤70% predicted and FEV_1/FVC <0.70 • mMRC dyspnea score ≥2	UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 TIO 18 24 weeks	Total: 843 214/173 212/181 209/165 208/177
374	Evaluate efficacy and safety over 24 weeks	R, DB, PG, AC	• COPD subjects ≥40 years • post-bronchodilator FEV_1 ≤70% predicted and FEV_1/FVC <0.70 • mMRC dyspnea score ≥2	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 TIO 18 24 weeks	Total: 869 215/166 217/163 222/165 215/176

Study Identifier	Study Objective(s)	Study Design	Key Enrollment Criteria	Once-Daily Treatment (mcg) (IH) Treatment Duration	Total Number of Subjects Randomized/ Completed
Long-term Safety Study					
359	Long-term safety	R, DB, PG, PC	• COPD subjects ≥40 years • post-bronchodilator FEV_1 ≥35% and ≤80% predicted and FEV_1/FVC <0.70	UMEC/VI 125/25 UMEC 125 Placebo 52 weeks	Total: 562 226/143 227/133 109/66
Exercise/Lung Function Studies					
417	Exercise endurance and lung function	R, DB, PC, XO	• COPD subjects ≥40 years • post-bronchodilator FEV_1 ≥35% and ≤70% • Resting FRC ≥120% • mMRC dyspnea score ≥2	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 UMEC 62.5 VI 25 Placebo 12 weeks	Total randomized/ completed: 348/258 completed: 132 131 44 43 64 148
418	Exercise endurance and lung function	R, DB, PC, XO	• COPD subjects ≥40 years • post-bronchodilator FEV_1 ≥35% and ≤70% • Resting FRC ≥120% • mMRC dyspnea score ≥2	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 UMEC 62.5 VI 25 Placebo 12 weeks	Total randomized/ completed: 307/217 completed: 112 117 33 38 56 120
UMEC Monotherapy Studies					
408	Safety and efficacy; dose selection	R, DB, PG, PC	• COPD subjects ≥40 years • post-bronchodilator FEV_1 ≤70% predicted normal and FEV_1/FVC <0.70 • mMRC dyspnea score ≥2	UMEC 62.5 UMEC 125 Placebo 12 weeks	Total: 206 69/62 69/56 68/50
589	Dose-ranging	R, DB, PC, PG	• COPD subjects ≥40 to ≤80 years • post-bronchodilator FEV_1 ≥35% to ≤70% of predicted and FEV_1/FVC ratio ≤0.70	UMEC 125 UMEC 250 UMEC 500 Placebo 28 days	Total: 285 71/65 72/68 71/64 71/67

Study Identifier	Study Objective(s)	Study Design	Key Enrollment Criteria	Once-Daily Treatment (mcg) (IH) Treatment Duration	Total Number of Subjects Randomized/ Completed
VI Monotherapy Studies					
206	Evaluate efficacy, safety, PK, and PD over 24 weeks	R, DB, PG, PC	• COPD subjects ≥40 years • post-bronchodilator FEV_1 ≤70% of predicted and FEV_1/FVC ratio ≤0.70 • mMRC dyspnea score ≥2 at Screening	FF/VI 50/25 FF/VI 100/25 FF 100 VI 25 Placebo 6 months	Total: 1029 206/147 206/151 205/145 205/142 207/138
207	Evaluate efficacy, safety, PK, and PD	R, DB, PG, PC	• COPD subjects ≥40 years • post-bronchodilator FEV_1 ≤70% of predicted and FEV_1/FVC ratio ≤0.70 • mMRC dyspnea score ≥2 at Screening	FF/VI 100/25 FF/VI 200/25 FF 100 FF 200 VI 25 Placebo 6 months	Total: 1224 204/144 205/158 204/155 203/160 203/161 205/146
871	Evaluate efficacy and safety including annual rate of moderate/severe exacerbations	R, DB, PG, AC	• COPD subjects ≥40 years • post-bronchodilator FEV_1 ≤70% of predicted and FEV_1/FVC ratio ≤0.70 • Exacerbation history (i.e. ≥1 exacerbation in previous 12 months)	FF/ VI 50/25 FF/ VI 100/25 FF/ VI 200/25 VI 25 12 months	Total:1622 408/315 403/312 402/301 409/294
970	Evaluate efficacy and safety including annual rate of moderate/severe exacerbations	R, DB, PG, AC	• COPD subjects ≥40 years • post-bronchodilator FEV_1 ≤70% of predicted and FEV_1/FVC ratio ≤0.70 • Exacerbation history (i.e. ≥1 exacerbation in previous 12 months)	FF/ VI 50/25 FF/ VI 100/25 FF/ VI 200/25 VI 25 12 months	Total: 1633 412/303 403/291 409/306 409/284
045	Evaluate efficacy and safety and dose-ranging	R, RD, DB, PG, PC	• COPD subjects ≥40 to ≤80 years • post-bronchodilator FEV^1 ≥35% to ≤70% of predicted and FEV_1/FVC ratio ≤0.70	VI 3.0 VI 6.25 VI 12.5 VI 25 VI 50 Placebo 28 days	Total: 602 99/88 101/91 101/92 101/92 99/91 101/85

Abbreviations: AC=active comparator; COPD=chronic obstructive pulmonary disease; DB=double-blind; FEV_1=forced expiratory volume in 1 second; FRC=functional residual capacity; FVC=forced vital capacity; IH=inhalation; mMRC=modified Medical Research Council; PC=placebo-controlled; PG=parallel-group; R=randomized; TIO=tiotropium; UMEC=umeclidinium bromide, VI=vilanterol; XO=cross-over.

Note: Treatments were administered once daily in the morning via the ELLIPTA dry powder inhaler (UMEC, VI, UMEC/VI or matching placebo) or the HandiHaler (tiotropium or matching placebo).

10.5. Adjudication of Fatal and Nonfatal Serious Adverse Reports

All SAE narratives, including deaths and hospitalizations, were adjudicated by an external independent, blinded adjudication committee for Phase IIIa studies in subjects with COPD treated with UMEC/VI or the UMEC component for at least 12 weeks to identify all on- and post-treatment respiratory- and CV-related deaths and hospitalizations occurring in these studies:

- Primary Efficacy Studies: studies 361, 373, 360, and 374
- Exercise/Lung Function Studies: studies 417 and 418
- Long-term Safety Study: study 359
- Other UMEC monotherapy Study: study 408

The adjudication was carried out on the case/report as a whole; thus, the case was adjudicated on the primary event (i.e., the event of the greatest medical significance, such as death, or hospitalization, or other reason for seriousness), not on every event comprising a particular case.

For all nonfatal SAEs, the adjudication included classification of the primary SAE according to the categories and subcategories provided in Table 88. The categories for nonfatal SARs differed from those for fatal SARs in that cancer was included only as a category for fatal SARs; also "sudden death" was not included as a subcategory under the CV category in the nonfatal SAR adjudication.

Table 88 Categories for Assignment of Primary Nonfatal Serious Adverse Reports

Primary Serious Adverse Report	Subcategory
Cardiovascular	Myocardial infarction/ischemic heart disease Congestive heart failure Stroke Haemorrhagic Thromboembolic Indeterminate Other cardiovascular cause
Respiratory	COPD exacerbation With evidence of pneumonia Without evidence of pneumonia Pneumonia/respiratory tract infection without COPD exacerbation Asthma associated Pulmonary embolism Other respiratory cause
Other	Not applicable
Unknown	Inadequate information Indeterminate

For all fatal SAEs, the adjudication committee members were asked to indicate the primary cause of death and further select a subcategory corresponding to the primary cause. In addition, the committee members were asked if the death was associated with the patients' known COPD. Table 89 gives the primary cause of adjudicated fatal SAR categories and subcategories.

Table 89 Categories for Assignment of Cause of Death for Adjudicated Fatal Serious Adverse Reports

Primary Cause of Death	Subcategory
Cardiovascular	Sudden death Myocardial infarction/ischemic heart disease Congestive heart failure Stroke Haemorrhagic Thromboembolic Indeterminate Other cardiovascular cause
Respiratory	COPD exacerbation With evidence of pneumonia Without evidence of pneumonia Pneumonia/respiratory tract infection without COPD exacerbation Asthma associated Pulmonary embolism Other respiratory cause
Cancer	Lung Breast Colorectal Unknown primary Other cancer cause
Other cause of death	Not applicable
Unknown	Inadequate information Indeterminate

10.6. Adverse Events of Special Interest: Groups, Subgroups, and Selection of Terms

Table 90 presents the special interest AE groups and subgroups for this program. Tabular presentations in this briefing document include only the events reported by one or more subject in the study or study grouping.

Table 90 Adverse Events of Special Interest: Special Interest Groups, Subgroups, and Selection of Terms

Special Interest AE Group	Special Interest AE Subgroup	Selection of Terms
Cardiovascular	Acquired Long QT	PTs: conduction disorder, electrocardiogram QT prolonged, long QT syndrome
	Cardiac Arrhythmia	Cardiac Arrhythmias SMQ
	Cardiac Failure	Cardiac Failure SMQ
	Cardiac Ischemia	Myocardial Infarction SMQ and Other Ischaemic Heart Disease SMQ
	Hypertension	Hypertension SMQ
	Sudden Death	PTs: sudden cardiac death, sudden death, cardiac arrest, cardio-respiratory arrest, and cardiac death
	Stroke	Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ
Effects on Glucose	Effects on Glucose	PTs: blood 1,5-anhydroglucitol decreased, blood glucose increased, diabetes complicating pregnancy, diabetes mellitus, diabetes mellitus inadequate control, diabetes with hyperosmolarity, diabetic coma, diabetic hepatopathy, diabetic hyperglycaemic coma, diabetic hyperosmolar coma, diabetic ketoacidosis, diabetic ketoacidotic hyperglycaemic coma, fructosamine increased, gestational diabetes, glucose tolerance impaired, glucose tolerance impaired in pregnancy, glucose urine present, glycosuria, glycosuria during pregnancy, glycosylated haemoglobin increased, hyperglycaemia, hyperglycaemic hyperosmolar nonketotic syndrome, hyperglycaemic seizure, hyperglycaemic unconsciousness, impaired fasting glucose, insulin resistance, insulin resistance syndrome, insulin resistant diabetes, insulin-requiring type 2 diabetes mellitus, ketoacidosis, ketonuria, ketosis, latent autoimmune diabetes in adults, metabolic syndrome, neonatal diabetes mellitus, pancreatogenous diabetes, type 1 diabetes mellitus, type 2 diabetes mellitus, urine ketone body present, abnormal loss of weight, abnormal weight gain, acidosis, anti-gad antibody positive, anti-insulin antibody increased, anti-insulin antibody positive, anti-insulin receptor antibody increased, anti-insulin receptor antibody positive, anti-islet cell antibody positive, blood glucose abnormal, blood glucose fluctuation, blood insulin abnormal, blood insulin decreased, blood lactic acid increased, blood osmolarity increased, body mass index decreased, body mass index increased, central obesity, coma, depressed level of consciousness, glucose tolerance decreased, glucose tolerance test abnormal, hyperlactacidaemia, hyperosmolar state, hyperphagia, hypoglycaemia, hypoinsulinaemia, impaired insulin secretion, increased appetite, increased insulin requirement, insulin autoimmune syndrome, insulin tolerance test abnormal, lactic acidosis, metabolic acidosis, obesity, overweight, polydipsia, polyuria, underweight, weight decreased, weight increased
Effects on Potassium	Effects on Potassium	PTs: hypokalaemia, hypokalaemic syndrome, hyperkalaemia, pseudohyperkalaemia
Tremor	Tremor	HLT of Tremor (excluding congenital)
Urinary Retention	Urinary Retention	PTs: urinary retention, urinary hesitation, micturition frequency decreased, urine flow decreased, Fowler's syndrome
Ocular Effects	Ocular Effects	Glaucoma SMQ and Visual Disorders NEC HLT
Gallbladder Disorders	Gallbladder Disorders	Gallbladder-related Disorders SMQ
Intestinal Obstruction	Intestinal Obstruction	Gastrointestinal Obstruction SMQ
Anticholinergic Effects	Anticholinergic syndrome	Anticholinergic Syndrome SMQ
LRTI and Pneumonia	Pneumonia	PTs: acute pulmonary histoplasmosis,

Special Interest AE Group	Special Interest AE Subgroup	Selection of Terms
		aspergilloma, aspergillosis, bacterial tracheitis, bronchiolitis, bronchitis, bronchitis bacterial, bronchitis fungal, bronchitis haemophilus, bronchitis moraxella, bronchitis pneumococcal, bronchitis viral, bronchopneumonia, bronchopneumopathy, bronchopulmonary aspergillosis, candida pneumonia, chronic pulmonary histoplasmosis, enterobacter pneumonia, enterobacter tracheobronchitis, fibrinous bronchitis, fungal tracheitis, hantavirus pulmonary infection, infective exacerbation of chronic obstructive airways disease, legionella infection, legionella test positive, lobar pneumonia, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection fungal, lower respiratory tract infection viral, lung abscess, lung consolidation, lung infection, lung infection pseudomonal, miliary pneumonia, mycobacterium test positive, necrotising bronchiolitis, organising pneumonia, pleural infection, pleural infection bacterial, pneumocystis jiroveci pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia blastomyces, pneumonia bordetella, pneumonia chlamydial, pneumonia cryptococcal, pneumonia cytomegaloviral, pneumonia escherichia, pneumonia fungal, pneumonia haemophilus, pneumonia helminthic, pneumonia herpes viral, pneumonia influenza, pneumonia klebsiella, pneumonia legionella, pneumonia measles, pneumonia moraxella, pneumonia mycoplasmal, pneumonia necrotizing, pneumonia parainfluenzae viral, pneumonia pneumococcal, pneumonia primary atypical, pneumonia respiratory syncytial viral, pneumonia salmonella, pneumonia staphylococcal, pneumonia streptococcal, pneumonia toxoplasmal, pneumonia tularaemia, pneumonia viral, pneumonitis, pseudomonas bronchitis, pulmonary echinococciasis, pulmonary mycosis, pulmonary mycotoxicosis, pulmonary sepsis, pulmonary trichosporonosis, pulmonary tuberculosis, pyopneumothorax, respiratory moniliasis, respiratory syncytial virus bronchiolitis, respiratory syncytial virus bronchitis, respiratory tract infection bacterial, rhinotracheitis, sinobronchitis, tracheitis, tracheitis obstructive, tracheobronchitis, tracheobronchitis mycoplasmal, tracheobronchitis viral, tuberculosis, viral tracheitis

Abbreviations: AESI=adverse event of special interest; HLT=high level term; LRTI=lower respiratory tract infection; MedDRA= Medical Dictionary for Regulatory Activities; NEC=not elsewhere classified; PT=preferred term; SMQ=standardized MedDRA Query

Note: Some AESI categories have been renamed for clarity in this briefing document. The AESI category called “Pneumonia” in the SDAP is referenced as “LRTI and pneumonia” to clarify that this category includes lower respiratory tract infections and related diseases. Also, the category called “Anticholinergic Syndrome” is referenced as “Anticholinergic Effects” since the Anticholinergic Syndrome SMQ which was used to locate terms includes events that are often associated with anticholinergic or antimuscarinic medications, but are not necessarily diagnostic for anticholinergic syndrome.

Note: Adverse events were coded using MedDRA version 15.0